Enantioselective synthesis of functionalised amino acids

Humphries, Mark Edward

Award date:
1999

Awarding institution:
University of Bath

Enantioselective Synthesis of Functionalised Amino Acids

submitted by Mark Edward Humphries

for the degree of PhD

of the University of Bath

1999

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Dedicated to my Mum and Dad

Acknowledgements

First and foremost I would like this opportunity to thank Professor Jonathan M. J. Williams my supervisor at the University of Bath, who has not only been a friend to me but has also been an excellent supervisor throughout my three years at Bath making the study a happy and enjoyable experience. I would also like to thank Dr. Barry Clark and Eli Lilly Pharmaceuticals for their help and encouragement, and of course, their financial contribution together with the University of Bath.

I would like to thank all the postgraduates and staff in the Chemistry Department at the University of Bath who made the environment a pleasant place to work. Special thanks goes to the postdoc's in the group; Kerry, Moharem, Christian and Dave Thomo', for all their help and advice. Thanks go to Phil Black and 'gym girl' Ruth for proof reading my thesis and the coffees had amid the hard graft of PhD work (in the gym!). To Jean-Philippe, my Gallic friend in the lab and on the rugby pitch at Combe Down RFC, thanks for being a good loser when Wales are victorious against France. For all the beers sunk, cheers to the Matt's (Ginger, Clarke and Lease), Amin, J-P, Kerry, the one and only 'Purple Gnome' Gian and the rest of the Williams' research group past and present. Lastly thanks to my flat mate Gail for generally being nice and putting up with me, and most importantly keeping me in a constant supply of biscuits throughout my writing up.

Finally I would like to say a huge thank you to my parents Ken and Joan for which, without their love and support I would not have been able to do this PhD. Thanks Mum and Dad.

Abstract

Diastereomeric enriched allylic amino esters have been prepared using the palladium catalysed allylic substitution reaction using prochiral palladium catalysts and enantiomerically pure amino esters. The reaction of *L*-amino methyl esters with the prochiral palladium catalyst ($[PdCl(C_3H_5)]_2$/dppe) affords allyl amine esters with up to 70% d.e.. Combining a matched pairing of enantiomerically pure amino ester with enantiomerically pure phosphinooxazoline ligand, results in enhanced selectivity of up to 90% d.e. Palladium catalysed allylic substitution has also been used to produce highly enantioselective allylic amines from diphenyl and bis methoxy phenyl allylic acetate substrates using the asymmetric phosphinooxazoline ligand **30a.** Oxidative cleavage of the alkene in the allylic amine product, with ruthenium tetraoxide or ozone, gives N-protected glycine analogues. Stereoselective epoxidation of the alkene in allylic amine, however, generates 3 adjacent chiral centres. Stereo- and regio- selective ring opening of the epoxide presents protected functionalised glutamic acids analogues. Ruthenium tetraoxide oxidation of the protected analogues in a solvent combination of ethyl acetate, acetonitrile and water, affords the N-protected amino acids in low yields. Over oxidation of the functionalised substrates with ruthenium tetraoxide prevents this enantiomeric synthesis being viable. Oxidation with ruthenium tetraoxide in the ethyl acetate, acetonitrile and water system gives comparable results to the standard Sharpless system (carbon tetrachloride, acetonitrile and water), providing a less hazardous alternative for the oxidative reaction.

Contents

Abbreviations

Ac	acetate
acac	acetylacetonate
ACE	angiotensin converting enzyme
Ar	aromatic ring
atm.	atmospheric pressure
Boc	*tert*-butoxycarbonyl
CNS	central nervous system
COSY	COrrelated SpectroscopY
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
d.e.	diastereomeric excess
DET	diethyl tartrate
DIAB	dimethylamino *iso*borneol
DMAP	dimethylaminopyridine
DMF	dimethylformamide
dppe	*bis* diphenylphosphinoethane
dppp	*bis* diphenylphosphinopropane
dppb	*bis* diphenylphosphinobutane
E	*entgegen*
EC_{50}	excitatory concentration for 50% maximum activity
EDCI	1-(3-methylaminopropyl)-3-ethylcarbodiimide hydrochloride
e.e.	enantiomeric excess
eq.	equivalent
Et	ethyl
EtOAc	ethyl acetate
FAB	Fast Atom Bombardment
FT	Fourier Transform
Glu	glutamate
h	hour

HMPA	hexamethylphosphorous triamide
HOBt	1-hydroxybenzotriazole hydrate
Hz	Hertz
*i*Bu	*iso*butyl
*i*Pr	*iso*propyl
J	coupling constant
m	*meta*
m	multiplet
*m*CPBA	*meta*chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mGluR	metabotrophic glutamate receptor
mmol	milli molar
mol.	molecular
nBu	normal-butyl
NaOMe	sodium methoxide
NMDA	*N*-methyl-*D*-aspartate
NMR	nuclear magnetic resonance
Nuc	nucleophile
o	*ortho*
OMe	methoxy
p	*para*
Ph	phenyl
PhthNK	potassium phthalimide
ppm	parts per million
*p*TSA	*para*-toluene sulfonic acid
q	quartet
R	*rectus*
S	*sinister*
t	triplet
*t*Bu	*tert*butyl
THAB	tetra-*n*-hexylammonium bromide
THF	tetrahydrofuran

TIPS-Tf	triisopropylsiloxyl triflate
tlc	Thin Layer Chromatography
$TMSN_3$	trimethylsilylazide
RT	Room Temperature
RuO_4	ruthenium tetraoxide
s	singlet
UV	Ultra Violet
Z	*zusammen*

Chapter 1

1 Introduction to Palladium Catalysed Allylic Substitution

1.1 Introduction

Transition metal catalysed reactions are now found in a wide range of synthetic transformations. Of the organometallic reagents, palladium complexes have arguably become the most important metal catalysts since their first use nearly forty years ago. Organopalladium chemistry started in the 1950's by the invention of the Wacker process.[1] Today, along with the Wacker process, the Heck,[2] Stille,[3] Suzuki[4] and allylic substitution[5] reactions have all made important contributions to the palladium success story.

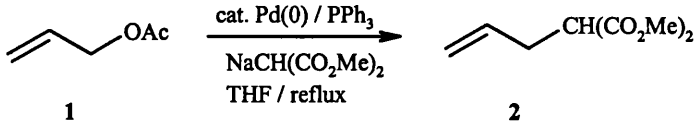
Palladium catalysed allylic substitution is now over thirty years old. It was first demonstrated by Tsuji[6] in 1965 that nucleophiles react with palladium allyl complexes, and since then intense research has been undertaken in the field. Allylic substitution reactions can now be carried out with high levels of stereo- and regioselectivity[5,7] and many other metal complexes (including platinum[8], rhodium[9], molybdenum,[10] cobalt,[11] iridium,[12] nickel,[13] tungsten,[14] iron[15] and ruthenium[16]) are able to catalyse the reaction. However, the palladium catalysed allylic substitution reactions still receive the greatest attention.

Initially, carbon nucleophiles were employed to form new C-C bonds.[17] However, with increasing interest in the reaction other nucleophiles have been investigated. These include; nitrogen,[18] sulfur,[19] oxygen,[20] phosphorus,[21]

silicon,[22] vinyl boranes,[23] hydrides,[24] tetraphenylborate[25] and organometallics such as dialkylzincs,[26] Grignards,[27] organoaluminium reagents,[28] organozirconium[29] and organotin reagents.[30] Of these, nitrogen has been widely exploited as many biologically interesting compounds and natural products can be accessed through this pathway.[31]

1.2 Reaction mechanism and scope

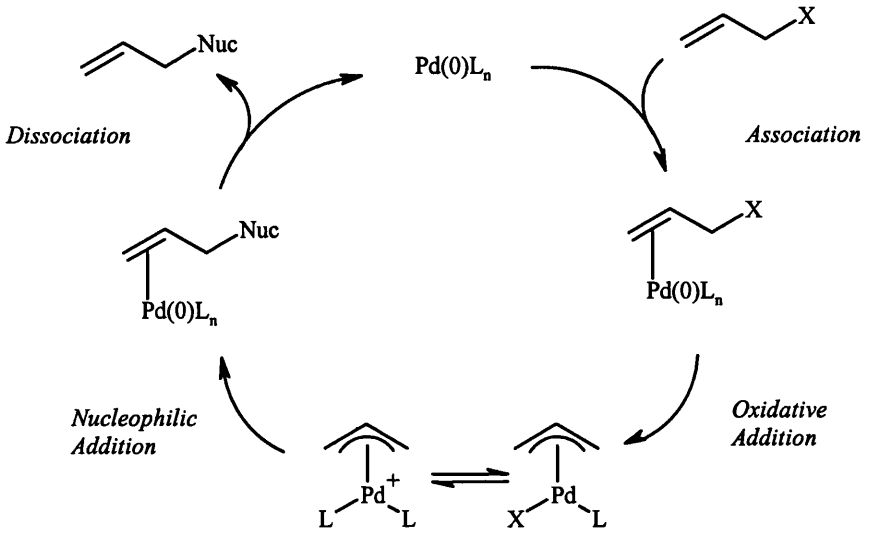
The basic process of palladium catalysed allylic substitution is illustrated below. Here the allylic acetate **1** is reacted with the sodium salt of dimethyl malonate in the presence of catalytic amounts of a palladium complex to give the substitution product **2**.[32]



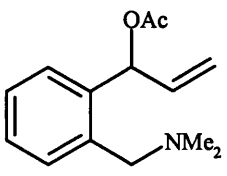
1 **2**

The mechanism is thought to proceed by complexation of a Pd(0) source to the alkene. On association of the palladium to the alkene, oxidative addition of palladium occurs (Pd(0) to Pd(II)) followed by loss of the leaving group to give a π-allyl complex. In the presence of phosphorus the π-allyl complex exists in equilibrium between the cationic and neutral species. The cationic form favours nucleophilic attack at one of the allylic termini, giving rise to the substitution product and regeneration of the Pd(0) active catalyst to continue in the catalytic cycle (Scheme 1.1).

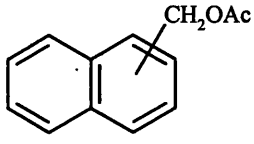
Scheme 1.1



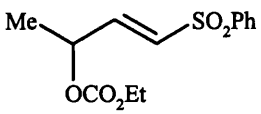
Palladium catalysed allylic amination reactions have been shown to be very tolerant to reaction variations. Acyclic straight,[33] branched[34] and cyclic[35] allyl systems have all produced impressive results. The methodology has been extended to intramolecular coupling,[36] (for example, the tertiary amine and allyl group of compound **3**), to naphthyl derivatives[37] (compound **4**) and to unreactive double bonds[38] (the γ-oxygenated vinyl sulfones **5**), thus illustrating the success of palladium catalysed allylic substitution.



3

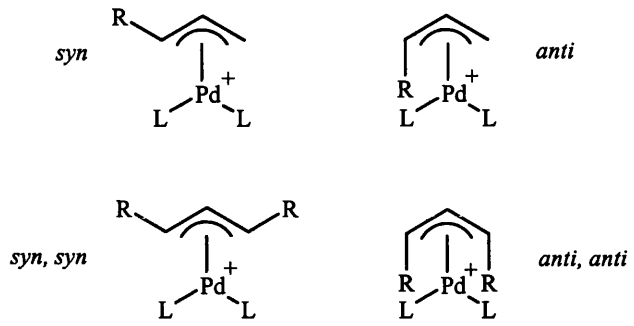


4



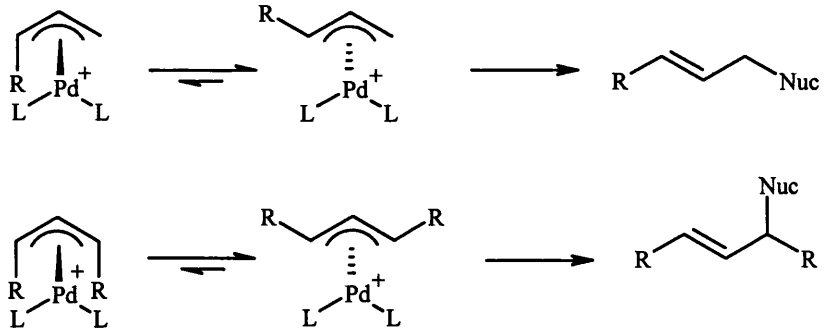
5

Scheme 1.2

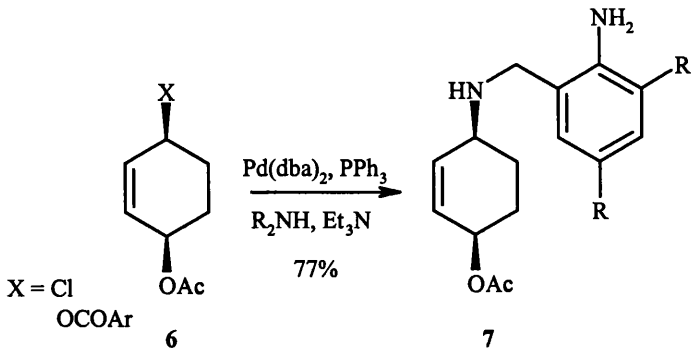


For open chain substrates the *syn* and *syn*, *syn* isomers are favoured over the *anti* and *anti*, *anti* forms due to steric constraints (Scheme 1.2). The isomeric forms can equilibrate by a π-σ-π mechanism in the catalytic cycle to form the most favoured conformation, thus giving the *syn*, *syn* isomers predominately (Scheme 1.3).

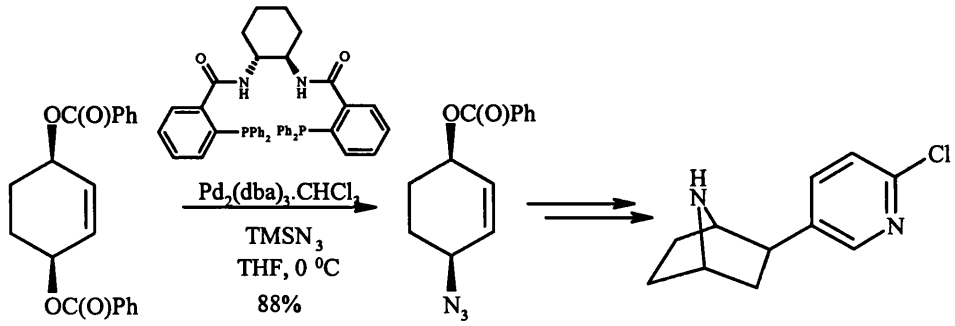
Scheme 1.3



Common leaving groups employed in the palladium catalysed substitution reaction are, acetates,[39] carbonates,[40] carbamates,[41] epoxides,[42] sulfones,[43] halides,[44] phosphates[45] and alkoxides.[46] Interestingly, Bäckvall has made use of the different properties of the leaving group. For example, substrates of type **6** have been successfully used to selectively form allylic amines such as compound **7** in an enantiodivergent synthesis of 4-aminocyclohex-2-enols.[47]



Trost has also shown that an enantioselective palladium catalysed allylic amination on *cis* 1,4-dibenzoyloxy-2-cyclohexene **8** gives desymmetrisation. Using stoichiometric amounts of nucleophile to substrate, only the mono-alkylated product **9** was formed, allowing an efficient synthesis of the non-opioid analgesic (-)-epibatidine **10**.[48]

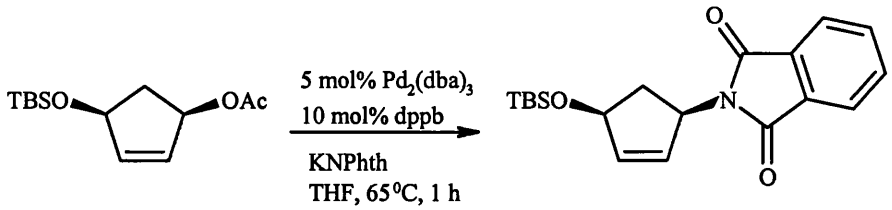


It is usual to use a Pd(0) species accompanied by a donor ligand such as phosphorus ($Pd(PPh_3)_4$, $Pd_2(dba)_3$-$2PPh_3$, $Pd(acac)_2$-$2PPh_3$).[45] The formation of bidentate ligand complexes has been shown to slow the isomerisation of *anti* and *syn* conformations in the π-σ-π mechanism. These complexes are therefore seen to be more advantageous when retention of stereochemistry at a chiral centre is important. The use of asymmetric ligands for enantioselective allylic alkylations has led to many other palladium complexes being used. The preparation of these

palladium catalysts is usually through pre-complexation of the ligand with a palladium source, such as $[PdCl(C_3H_5)]_2$ or $Pd_2(dba)_3$, before addition to the reaction.

Primary and secondary nitrogen nucleophiles work well, giving excellent results with a wide range of substrates.[34,36,47,49] Ammonia however, cannot be applied to palladium catalysed reactions because of polyallylation resulting in contamination with secondary and tertiary allyl amines. To overcome this, ammonia synthons are used. Primary allyl amines are available through the use of nucleophiles such as phthalimide,[50] di-*tert*-butyl iminodicarbonate,[51] *p*-toluenesulfonamide,[52] azide,[53] dialkyl N-(*tert*-butoxycarbonyl)-phosphoramide.[54]

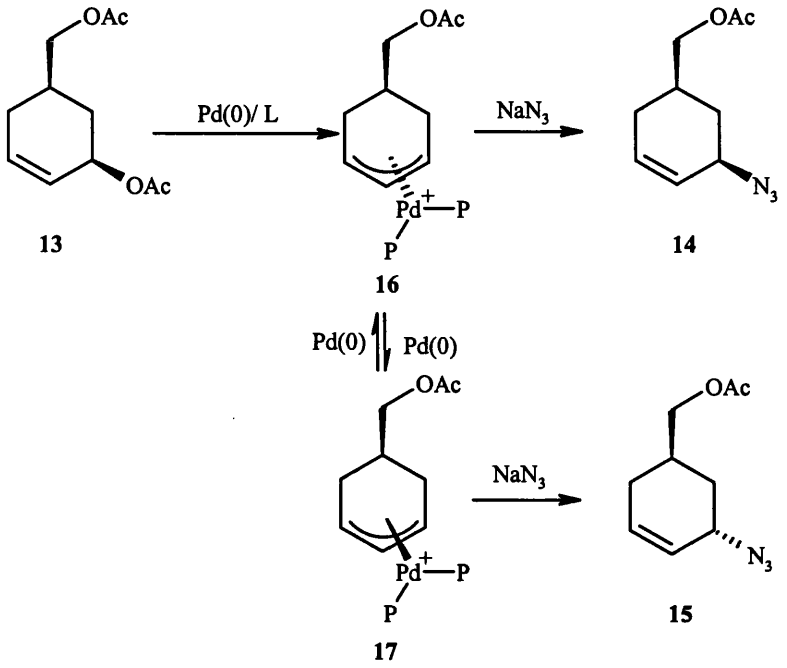
It has been demonstrated in a number of studies that a chiral allylic acetate will show retention of stereochemistry in a palladium catalysed substitution using soft nucleophiles.[47,49,55] The amination of chiral acetate **11** with the soft nucleophiles, phthalimide or benzylamine and a $Pd_2(dba)_3$/dppb catalyst proceeds with overall retention of stereochemistry to give the (*R*) allylic amine **12**.[49]



11 85% **12**

Murahashi *et al* have shown however, that the palladium catalysed azidation of **13** gave different isomeric ratios of **14** and **15** when the mono-dentate ligand PPh_3 (**14/15** ratio 54:46) was used instead of the bidentate ligand dppb (**14/15** ratio 93:7).[56] These stereochemical outcomes can be rationalised by two sequential

inversion steps in the mechanism. The mechanism for overall retention is as follows; the palladium displaces the leaving group with inversion, followed by nucleophile attack on the *exo* face, again with inversion. Overall, this accounts for the net retention of stereochemistry in the product.



Several mechanisms have been suggested to account for the loss of stereoselectivity:

i) isomerisation of starting material

ii) *syn* addition of nucleophiles

iii) isomerisation of product

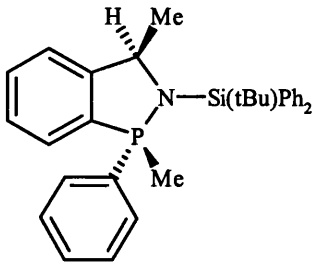
iv) Pd(0) catalysed isomerisation of the intermediate π-allyl complex.

Work by Bäckvall and co-workers has demonstrated that *exo* attack of a Pd(0) complex to the intermediate π-allyl complex is the major reason for isomerisation between the *anti* and *syn* complexes **16** and **17**.[57] Subsequent nucleophilic attack

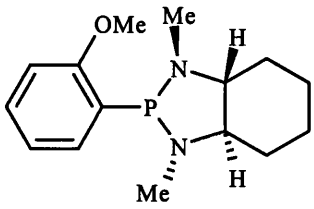
gives rise to a mixture of isomers. Isomerisation by Pd-Pd displacement can be minimized by using a reactive substrate, lowering the Pd(0) concentration or, as Murahashi found,[56] by using a bidentate ligand. The use of monodentate ligands such as PPh_3, seems to allow the isomerisation of the π-allyl complex to proceed faster, thus diminishing the stereochemical purity of the enantiomerically enriched substrate.

1.3 Ligands in palladium catalysed allylic substitutions

The generation of an asymmetric centre from a racemic allyl starting material utilising the palladium catalysed allylic substitution reaction, is a goal that interests many research groups. Directing nucleophilic attack selectively to one of the termini of the π-allyl complex enables enantioselectivity to be introduced into the allylic amine. By far the most popular approach to generate enantioselectivity in the substitution reaction is to use directing ligands. The most successful asymmetric ligands developed to date have been bidentate structures incorporating diphosphines, diamines or mixed heteroatoms. The highest reported asymmetric induction for a monodentate ligand, however, has been with the chiral phosphorus catalysts **18** and **19**, developed by Wills and co-workers.[58,59]

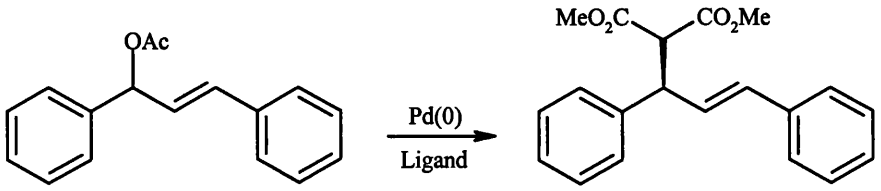


18



19

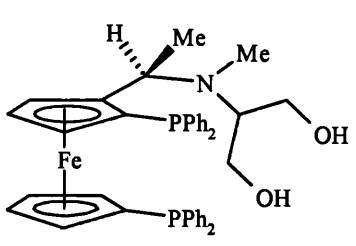
For the invariably standard transformation, (*E*)-1,3-diphenylprop-2-enyl-1-acetate **20** to 1,3-diphenylpropyl dimethylmalonate **21** with sodium dimethyl malonate as nucleophile, ligand **18** gives a very respectable e.e. of 91.5%. Aminations with the phosphorus ligand **19** are also impressive, giving enantioselectivities of up to 78% with benzylamine as nucleophile.



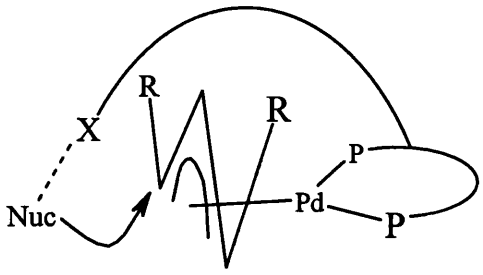
20 **21**

Over a decade ago Hayashi first developed the chiral ferrocene ligand **22**. Using diphosphine donor atoms and a pendant side chain bearing a functional group at the terminal position, asymmetric inductions with amine nucleophiles were attempted.[60] The terminal functional group is expected to interact with the incoming nucleophile, directing attack to one of the π-allyl carbon terminals selectively (Scheme 1.4).

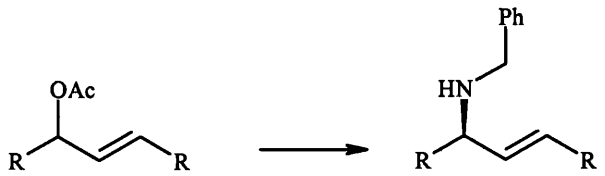
Scheme 1.4



22



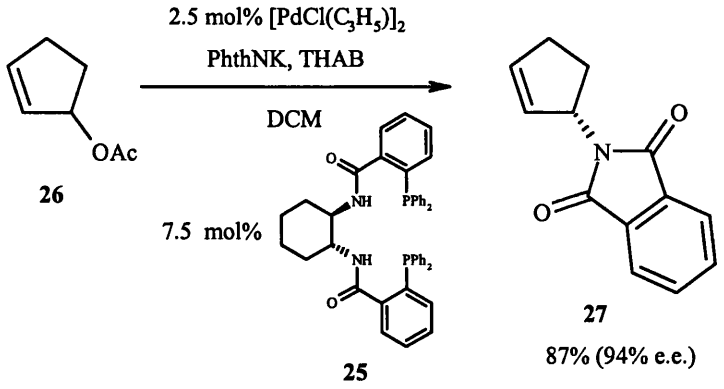
Using substrate **23** (R=Ph) with benzylamine as nucleophile, and the catalyst of $Pd_2(dba)_3.CHCl_3$ / ligand **22**, enantioselectivities of up to 97% were observed. Hayashi found that the pendant hydroxy group needed to be four atoms away from the ferrocenylmethyl position to obtain these excellent selectivities. The palladium catalyst incorporating the diphosphine **22** was also shown to be an effective catalyst for the allylic acetates **23**, where R= *i*Pr, *n*Pr or Me affording the allylic amine **24** in 97%, 82, and 73% e.e. respectively.



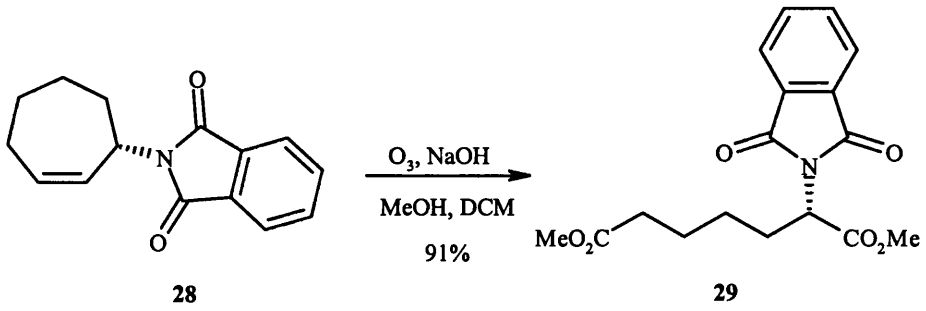
23 R = Ph
Me
iPr
nBu

24

Trost's chiral diphosphine ligand **25** has proven to be the superior ligand for asymmetric inductions when cyclic substrates are used.[61] The dome type architecture that controls the stereochemistry in the reaction is primarily a steric consideration. Trost discovered that in the palladium catalysed amination of cyclic allylic acetates, such as 3-acetoxycyclopentene **26** with potassium phthalimide, the counter-ion was of great importance with respect to the enantioselectivity. Optimum results were obtained when using tetrahexylammonium salt as the counter-ion affording the substitution product **27** with enantioselectivities of 93-98%.



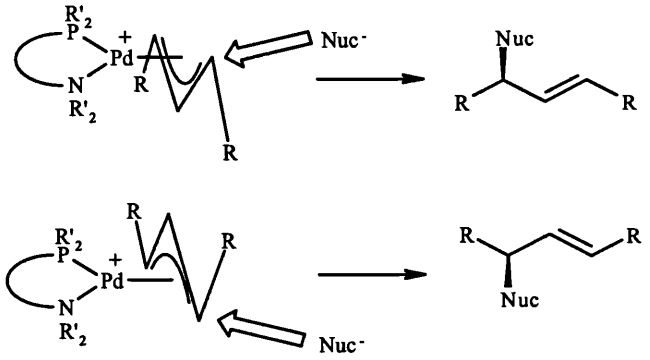
Excellent selectivity is observed with ligand **25** on a range of ring sizes allowing natural and unnatural amino acids to be prepared, including the inhibitor of Gram-negative active bacteria, (*S*)-2-aminopimelic acid **29** derived from the seven membered ring **28**.



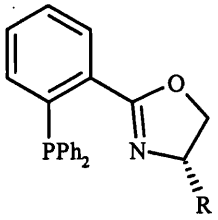
An alternative approach for the design of asymmetric ligands is to have two electronically different ligating groups on the bidentate structure to partly determine the stereochemical outcome. Research by Åkermark, Vitagliano and co-workers[62] established that the reactivity of palladium allyl complexes vary substantially when bidentate phosphine and bidentate nitrogen ligands were employed. However, more importantly, they observed that when mixed phosphorus/nitrogen donor ligands were used, the allyl terminus *trans* to the π-accepting phosphorus atom was more electrophilic than the position *trans* to the nitrogen atom. Thus, it can be expected that the nucleophile would approach the

palladium allyl intermediate *trans* to the π-accepting phosphorus. So if ligand design could control the orientation of the intermediate complex in either the 'M' or the 'W' conformation for nucleophilic attack, determination of the stereochemical outcome of the substitution product could be controlled (Scheme 1.5).

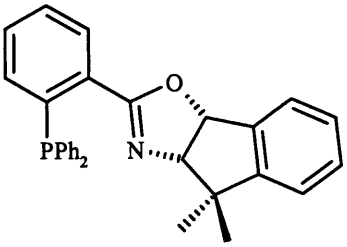
Scheme 1.5



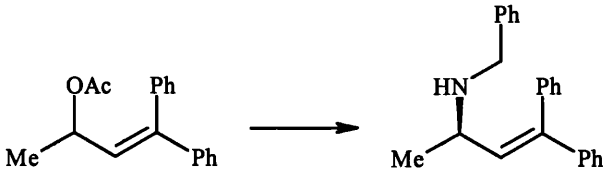
To this end, independent work by the groups of Williams,[63] Pfaltz[64] and Helmchen[65] have designed such ligands to do this job. The asymmetric ligands **30a-c** consisted of phosphorus/nitrogen mixed donor atoms for chelation control and an oxazoline unit to control the orientation of the allyl group and give the chirality control. With the diphenyl substrate **23** (R=Ph) the asymmetric inductions are extremely impressive, giving excellent e.e.'s with a range of nucleophiles. Oxazoline ligands **30a-c** have also given excellent e.e.'s using carbon nucleophiles with unsymmetrical substrates of the type **32**. However, the less reactive nitrogen nucleophiles do not give substitution products with the more sterically crowded substrate **32**.



R = iPr **30a**
Ph **30b**
tBu **30c**



31

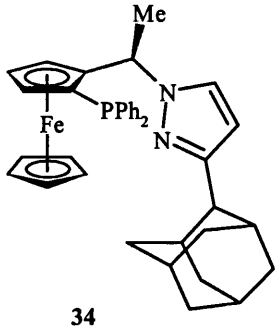


32 **33**

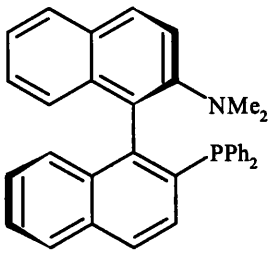
The success of the phosphorus containing oxazoline ligand **30** in palladium catalysed asymmetric alkylations and other metal catalysed enantioselective reactions has led to the development of similar mixed phosphorus/nitrogen ligands containing the oxazoline moiety. Of the subsequent ligands produced, one of the better examples is ligand **31** where the two conformationally fixed methyl substituents give the stereocontrol in the allylic amination, achieving high e.e.'s (97% with benzylamine and 98% with phthalimide) with substrate **23**.[66] Allylic amine **33** can also be produced using the ligand **31** from the allylic acetate 1,1-diphenyl-2-buten-3-yl acetate **32** (previously reported by Williams *et al*, not to react with the oxazoline ligand **30**[67]).

For the phosphorus/nitrogen donor atom ligands, other good examples are, Togni's ferrocenyl ligand **34** containing phosphine and pyrazole units,[68] Kocovsky's binaphthyl class of P,N ligands **35**,[69] and the chiral pyridine-phosphine ligand **36**.[70] Extremely high enantioselectivity is achieved (>99%)

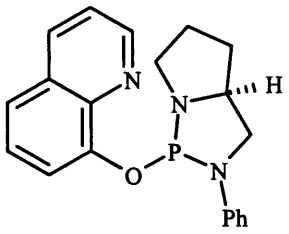
with ligand **34** in the allylic substitution of acetate **23** with benzylamine, illustrating the interplay of steric and electronic properties in these ligands to achieve stereocontrol. The P,N ligand **35** has both the chelating atoms directly fixed onto the aromatic scaffold to determine the selectivity. The chirality of ligand **36** is generated from a chiral phosphorus donor atom and generates enantiomeric excesses of up to 94% with amine nucleophiles.



34

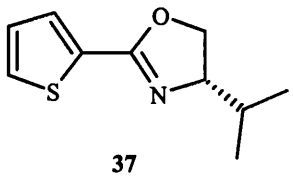


35



36

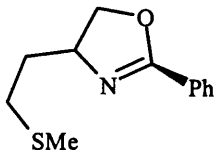
Phosphorus and nitrogen are not the only combinations for mixed donor atom ligands that have been successfully combined in palladium catalysed alkylations. Sulphur has been used as an auxiliary binding site instead of phosphorus. Williams first designs of chiral ligands[71] focused on the thienyl oxazoline **37** which indeed gave good yields (89%) and e.e.'s (81%). Weak binding of sulfur to palladium and poor reactivity of the thienyl ligands eventually directed research to the now well documented phosphine oxazoline ligands.



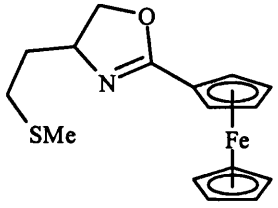
37

Research on sulfur containing ligands in other research groups continued and several ligands have been reported which give impressive stereoselectivities in

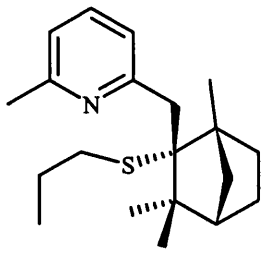
allylic alkylations. Bryce *et al* have used the designs of Williams ligand **38,**[72] which itself gave a very respectable 88% e.e. in 79% yield, to come up with the ferrocenyl derivative **39**. This delivers, for the test bed reaction of 1,3-diphenyl prop-2-enyl acetate **20** to 1,3-diphenyl prop-2-enyl dimethyl malonate **21**, an improved enantiomeric excess of 93% in a nearly quantitative yield of 98%.[73] Impressive enantioselectivities, 93%-98% e.e. with yields greater than 94%, are also observed with the chiral pyridine thiols **40**, designed by Kellogg, for the same reaction.[74]



38

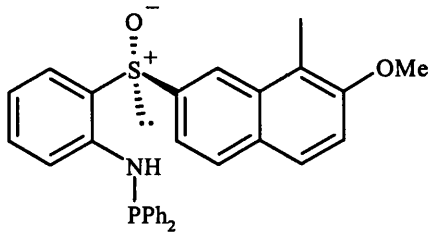


39



40

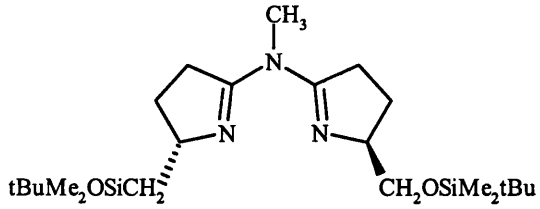
Mixed donor atoms with two strongly binding atoms, such as phosphorus and sulfur, have also be used; Hiroi's ligand **41** can induce asymmetric palladium catalysed substitution with excellent enantioselectivities (97%).[75]



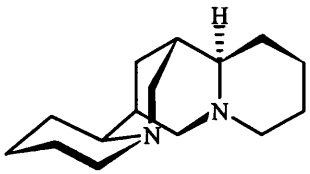
41

Diamine complexes may have weaker binding properties than phosphorus containing ligands, but they were the focus of initial research by Pfaltz and Togni. Pfaltz obtained very good e.e.'s with his C_2-symmetric 5-aza-semicorrin ligands

42 in palladium catalysed alkylation and cyclopropanation reactions of olefins, utilising the rigid scaffold structure to hold the metal in close proximity of the two stereogenic substituents to influence the stereochemical outcome.[76] Togni's diamine sparteine complexes **43**[77] proved to be less successful compared to the *bis*-oxazolines by Pfaltz, nevertheless, respectable enantioselectivities were achieved (75%) in good yields.

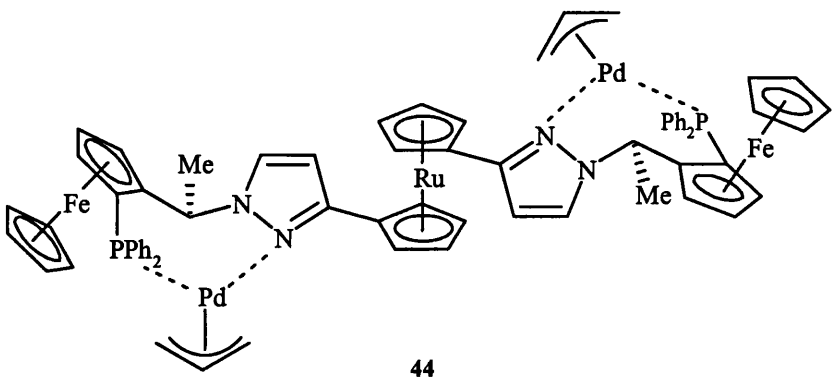


42



43

The array of asymmetric ligands is now vast, and while better ligands are still being produced, new methods to improve turnover rates and regeneration of the active catalyst are generating greater interest in this field. Togni with his ferrocenyl P,N ligands has explored the coupling of two catalytic sites by a bridging ferrocenyl or ruthenocenyl linker, with the goal of attaining a multi centre catalyst. The performance of the bimetallic catalytic complex **44** in terms of activity and enantioselectivity was analogous to that of the mononuclear system, however, the lower solubility of the dimer gives potential for better recovery.[78]

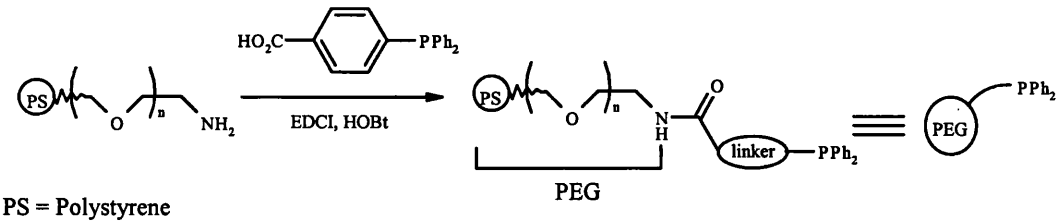


44

Finally, solid phase chemistry is entering the area of palladium catalysed allylic substitution. Hayashi has successfully carried out substitution reactions on a range of substrates with carbon and amine nucleophiles using a palladium phosphine complex bound to an amphiphilic polymer resin, based on a polyethylene glycol-polystryrene graft copolymer (Scheme 1.6).[79] Excellent yields were achieved in the reaction while the solid phase catalyst is readily recovered by filtration with no loss of catalytic activity for seven continuous runs. Even though these allylic alkylations, carried out in an aqueous medium, were not enantioselective, it is only a matter of time before advances are made to produce the asymmetric variant.

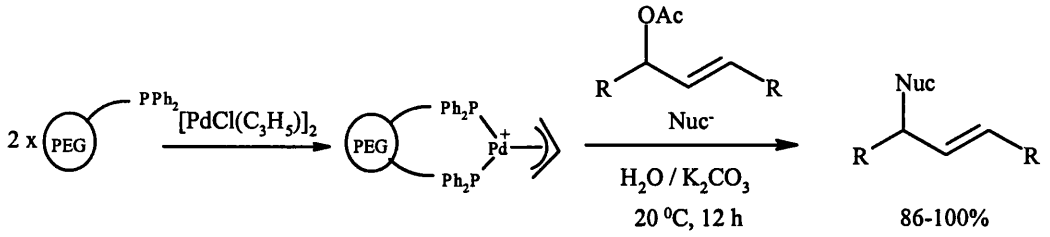
Scheme 1.6

Preparation of catalyst:



PS = Polystyrene
PEG = Glycol-polystyrene graft

Palladium catalysed allylic substitution:



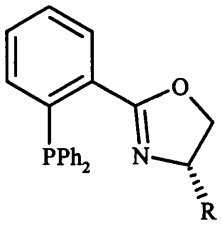
Chapter 2

2 Palladium Catalysed Asymmetric Amination

2.1 Introduction

Allylic amination using palladium catalysts is well documented for incorporating a nitrogen atom into a molecule. In the mid 1980's palladium catalysed allylic amination methodology increased its potential by the extension into enantioselective variants. Development of directing ligands, pioneered by Hayashi,[60] became the major player in enantiocontrol of reactions.

In Chapter 1 we observed the different ligand designs used to control the selectivity. For the phosphinooxazoline ligand **30a**, designed by Williams, Pfaltz and Helmchen, the different electronic properties of the phosphorus and nitrogen donor atoms, and the formation of an allyl palladium complex is an important part of the palladium catalysed reaction. Substrates are often chosen so they proceed *via* a symmetrical allyl palladium complex.

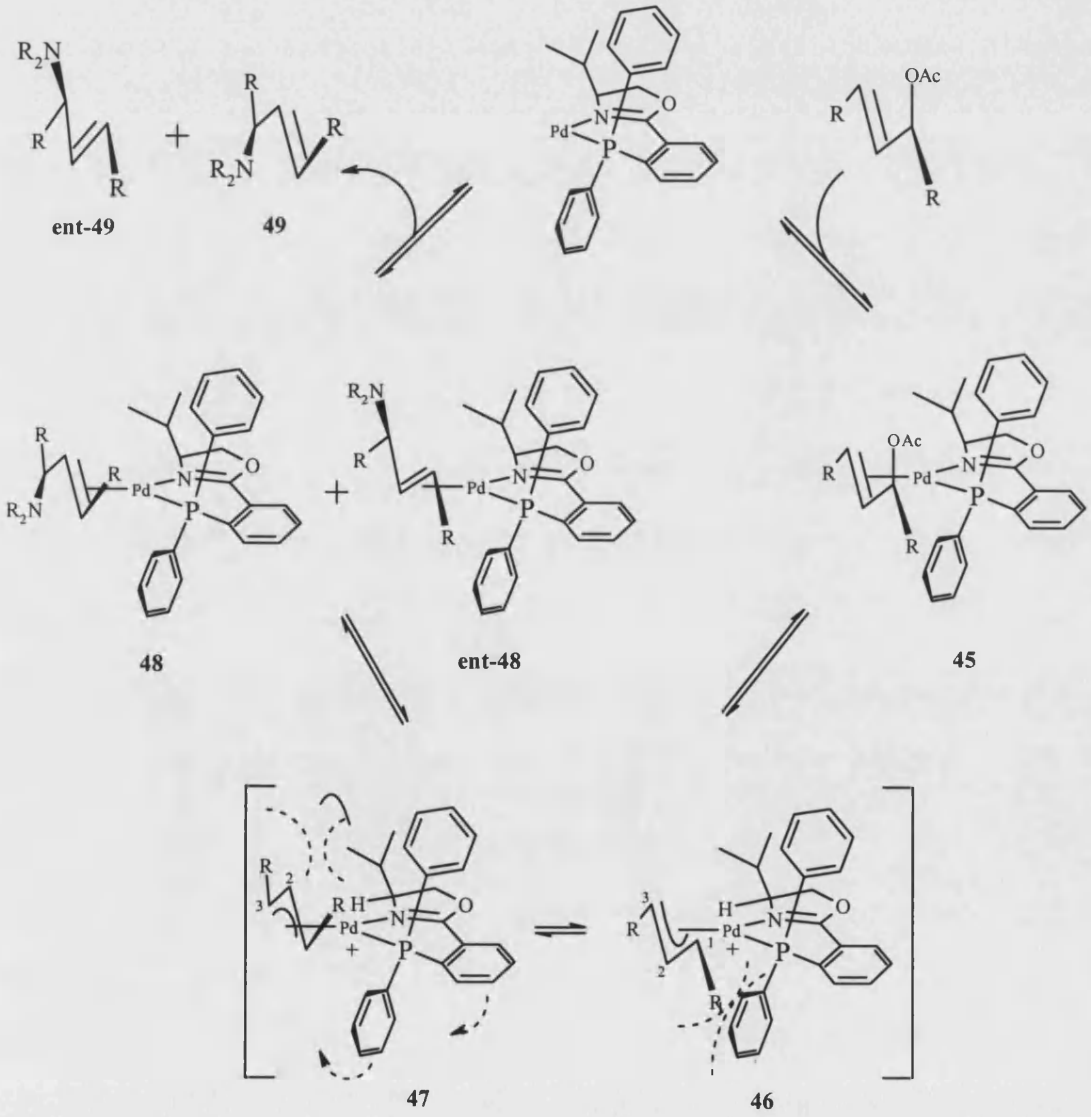


30a R = iPr
30b R = Ph
30c R = tBu

Scheme 2.1 illustrates the Pd/ligand sequence in the nucleophilic substitution. On oxidative addition of the alkene to the palladium complex **45**, the π-allyl complex

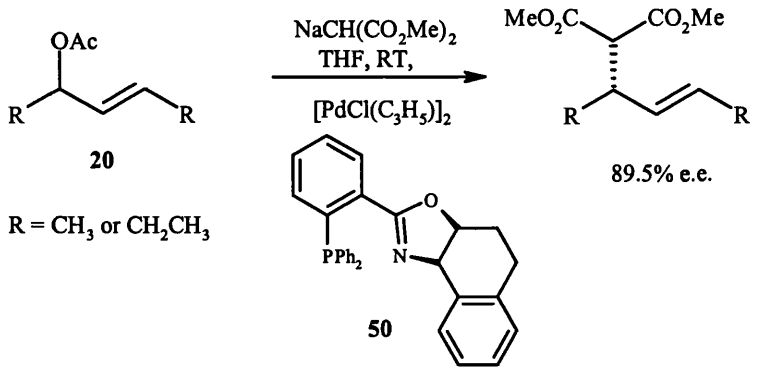
can adopt two configurations, the 'M' orientation **46** and the 'W' orientation **47**.[80] Nucleophilic attack at position 3 (*trans* to phosphorus) will result in either of the Pd^0-alkene complexes **48** or **ent-48**, depending on which intermediate **46** or **47** is more reactive towards the nucleophile. Dissociation of the Pd^0-complex then gives the allylic amine product and the active palladium catalyst ready to enter the cycle again.

Scheme 2.1



Helmchen and co-workers[81] showed in a series of X-ray crystallographic and NMR studies, that complex **47** was the most reactive and the major diastereoisomer in equilibrium. The isopropyl group on the oxazoline moiety is seen to be pseudoequatorial, and it is the neighbouring hydrogen atom that favours the 'W' orientation **47.** The size of the group at the stereogenic centre of the oxazoline affects the enantiocontrol of the reaction, through the repulsion between the phenyl rings at phosphorus and their interactions with the R group of the π-allyl system. Repulsion of the phenyl rings at phosphorus relays distortion along the N-C-C-C-P plane of the ligand, bending the phosphorus phenyl rings towards the R group of the substrate, increasing interaction and disfavouring complex **46**.

Although phosphinooxazoline **30** is an excellent ligand for substrates with large R groups such as 1,3-diphenylprop-2-enyl acetate, which allows strong repulsion between substrate and catalyst, smaller acyclic substrates and cyclic variants produce products with much lower enantioselectivities.[82] To overcome these short falls, Helmchen designed a new ligand, oxazoline **50**, to succeed with these smaller substrates. In phosphinooxazoline **50,** a conformational restricting ring incorporated into the oxazoline unit, replaces the isopropyl group and maximises the steric interaction between the R group and the palladium ion ligand. These new sterically demanding ligands have produced enantioselectivities in the substitution reaction of sodium dimethylmalonate with substrates pent-2-enyl and hept-2-enyl acetates with up to 89.5% e.e..[83]



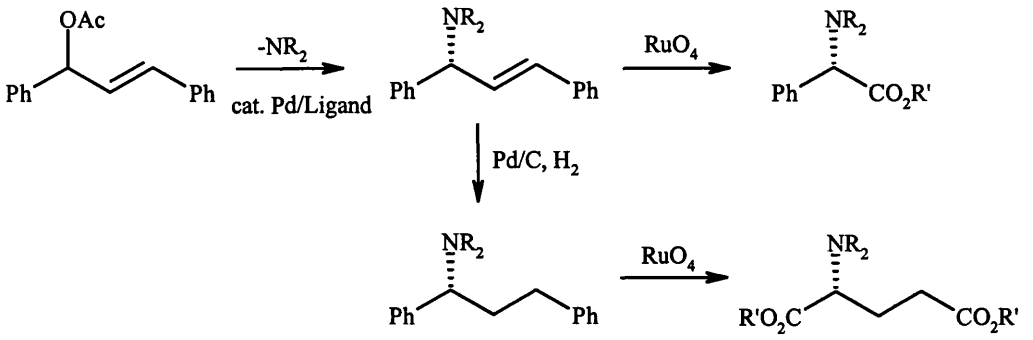
The enantioselective palladium catalysed allylic amination utilising the oxazoline ligand **30** is well established. Using the 1,3-diphenylprop-2-enyl acetate **20**, this research group[84] and others[85] have shown excellent enantioselectivities can be achieved with various nitrogen nucleophiles (Table 2.1).

Table 2.1 Enantioselectivities for the allylic amination of 1,3-diphenylprop-2-enyl acetate **20**.

Nucleophile	Ligand	Temp. (°C)	Time (h)	Yield (%)	e.e. (%)
PhthNK[84]	30a	50	48	91	96-98
TsNHNa[84]	30a	50	24	90	95
TsNHNa[85]	30c	50	48	96	97
$(Boc)_2NNa$[84]	30a	50	24	90	54
$(Boc)_2NNa$[85]	30c	50	96	90	67
PhCONHNHNa[85]	30c	50	96	95	97
$PhCH_2NH_2$[85]	30c	23	96	87	89

The resulting allylic amines are synthetically useful compounds. Williams *et al* [84] have shown that enantiomerically enriched α-amino acids (glycine and glutamic acid) can be prepared by oxidative cleavage of the olefin or by reduction of the alkene followed by oxidative cleavage of the phenyl rings (Scheme 2.2).

Scheme 2.2

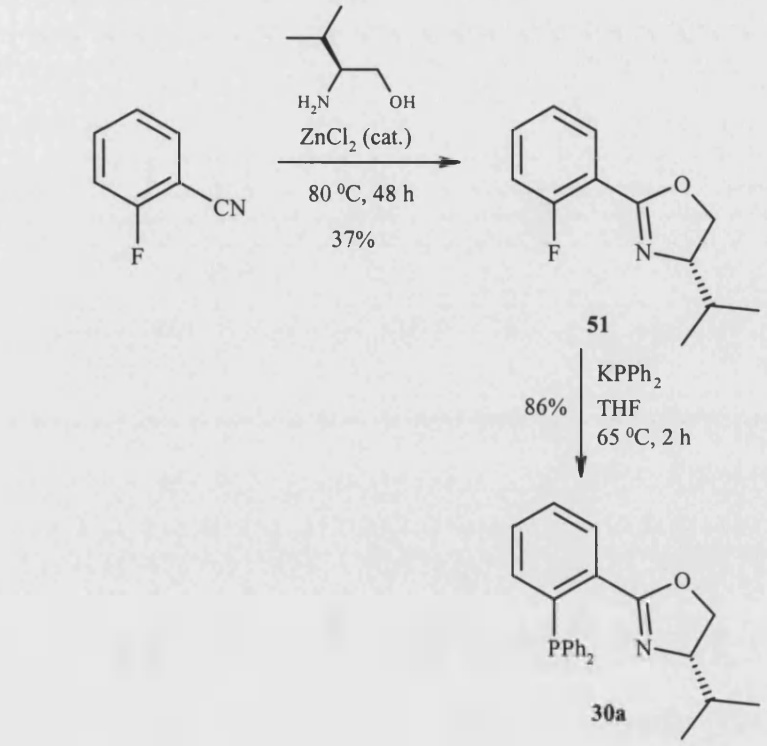


Our interest was in further extending this methodology to different nitrogen nucleophiles and allylic substrates. The best enantiomeric excesses previously have been reported with the potassium salt of phthalimide[84] and the aspect that we wanted to pursue was to find nitrogen nucleophiles that give as impressive e.e. as phthalimide but would be easier to remove. Also, deviating from the diphenyl allylic acetate substrates to other aromatic groups, offered an alternative, where the methodology could be used to prepare unnatural amino acids.

2.2 Synthesis of phosphinooxazoline ligand 30a and ent-30a

The enantiomerically pure phosphinooxazoline ligand **30a** was prepared from the fluorooxazoline **51**. Heating 2-fluorobenzonitrile with (*R*)-valinol in the presence of catalytic amounts of zinc chloride at 80 °C for 48 hours gave the oxazoline **51** in 37% yield. The phosphinooxazoline **30a** was formed from the halide by addition of potassium diphenylphosphide in THF to a refluxing solution of the fluorooxazoline **51** and THF. After 2 hours of heating the phosphinooxazoline was isolated in 86% yield. The corresponding **ent-30a** ligand was prepared in an analogous manner from (*S*)-valinol and fluorobenzonitrile. Crystallisation of **ent-**

30a from ethyl acetate and light petroleum gave colourless bricks of ligand **ent-30a**, Figure 2.1.



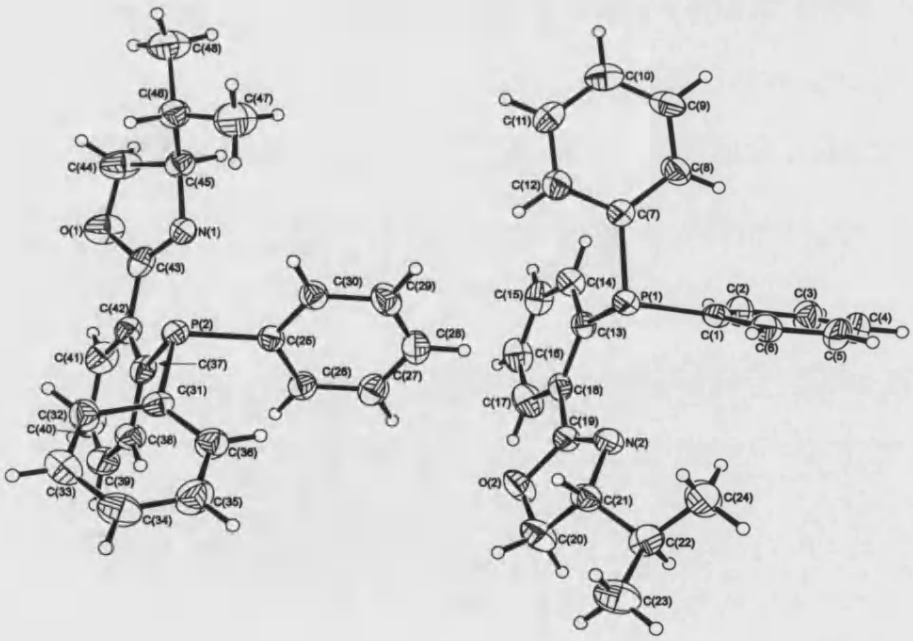
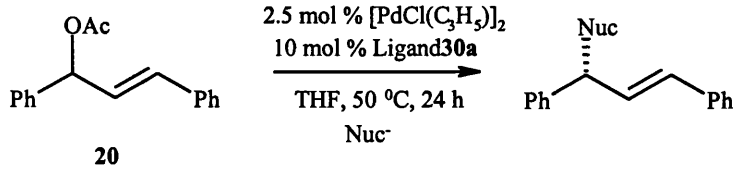


Figure 2.1 Crystal structure of **ent-30a** showing the labelling scheme used. Thermal ellipsoids are represented at the 30% probability level (for supplementary data to Figure 2.1 see Appendix A)

2.3 Nitrogen nucleophiles in palladium catalysed substitution

Allylic substitution of racemic 1,3-diphenylprop-2-enyl acetate **20**[86] with nitrogen nucleophiles **52-60** in the presence of catalytic amounts of allyl palladium chloride dimer and the oxazoline ligand **30a** only gave the substitution products **61** and **62**.

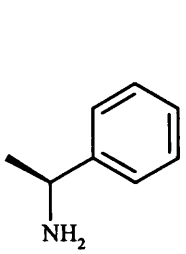


20

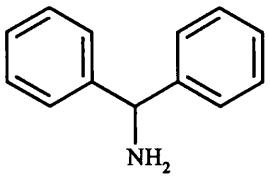
61 Nuc = $NHCH(CH_3)Ph$ 84% (24% e.e.)
62 Nuc = $NHCH(Ph)_2$ 81% (78% e.e.)

Low enantioselectivity (24% e.e.) is observed with α-methyl benzylamine **52**; increasing the size of the substituent at the α-position from a methyl group to a phenyl ring, diphenylmethylamine **53**, increases the selectivity to 78% e.e.. However, extending the logic further by addition of another phenyl substituent at the α-position, tritylamine **54,** causes too much steric crowding for the nucleophile to successfully attack the π-allyl system and no substitution product is observed. The same argument was applied to the bulky chiral nucleophile **55** where similarly no product was observed.

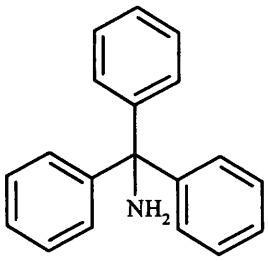
The tetrachlorophthalimide salt **60** was seen as a good alternative to phthalimide; still retaining a similar profile to phthalimide while offering an easier way of removal.[87] The introduction of four electron withdrawing chloride atoms to the aromatic ring however, makes the amine far less nucleophilic and no substitution product was detected in the reaction mixture.



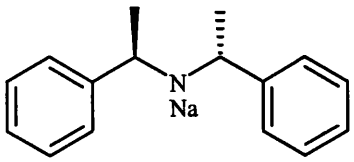
52



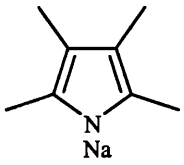
53



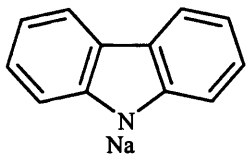
54



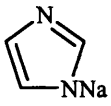
55



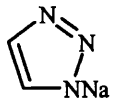
56



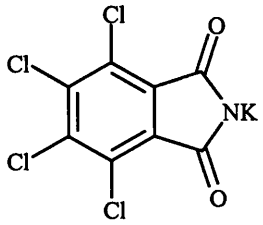
57



58



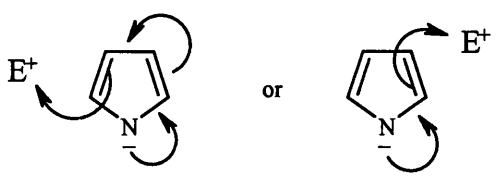
59



60

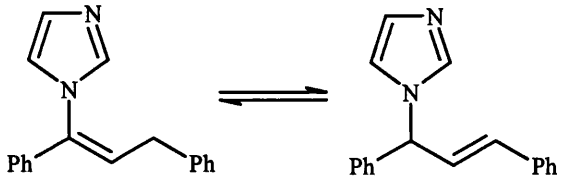
Using the planar structure of phthalimide as a basis of nucleophile selection, the nitrogen heterocycles tetramethylpyrrole **56** and carbazole **57** were explored as possible candidates. In anticipation of a pyrrole salt attacking from position 2' or 3' of the aromatic ring (Scheme 2.3), tetramethylpyrrole was chosen in order to try and cause a steric obstacle for these pathways.

Scheme 2.3

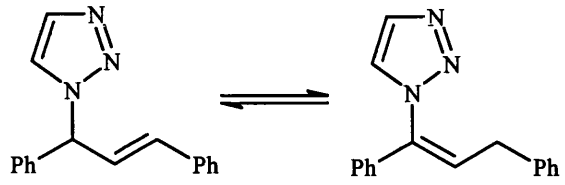


The NMR data of the main product from the reaction with nucleophile **56** gave a complex mixture of signals between δ1-3, assigned to methyl groups on the pyrrole ring, indicating a mixture of substitution products. The carbazole nucleophile **57** can be seen as a pyrrole unit with conformational and steric restrictions imposed by the phenyl rings. These had little effect on the outcome, illustrating that N-alkylation of pyrrole anions is a much higher energy pathway for nucleophilic substitution than C-alkylation. Alternatively, changing the electronic nature of the heterocycle by increasing the number of nitrogen atoms in the aromatic ring was proposed. This also increased our chances of alkylating at nitrogen. The sodium salts of imidazole **58** and triazole **59** were explored in the palladium catalysed substitution reaction and in both reactions two products were observed.

Analysis of the ^{1}H and ^{13}C NMR data for the imidazole reaction, applying ^{1}H-^{1}H and ^{13}C-^{1}H COSY techniques, strongly suggested that the major fraction (isolated in 21%) was compound **63**. A doublet of intensity two at δ3.37, a proton triplet at δ6.30 and three coupled singlets in the aromatic region at δ6.88, δ7.19 and δ7.55 (imidazole protons) in the ^{1}H NMR, together with the mass spectrum of M^{+} 260 confirmed the substitution product as heterocycle **63**. The minor component (isolated in 15%) from the reaction is in agreement with structure **64**, (tautomer of **63**) where the olefin signals of a doublet at δ6.39 and a doublet of doublets at δ6.50 are observed together with a doublet for the CHN proton at δ5.88. Similar spectroscopic data was seen in the reaction of triazole **59** giving the tautomers **65** (17%) and **66** (23%).



63 **64**

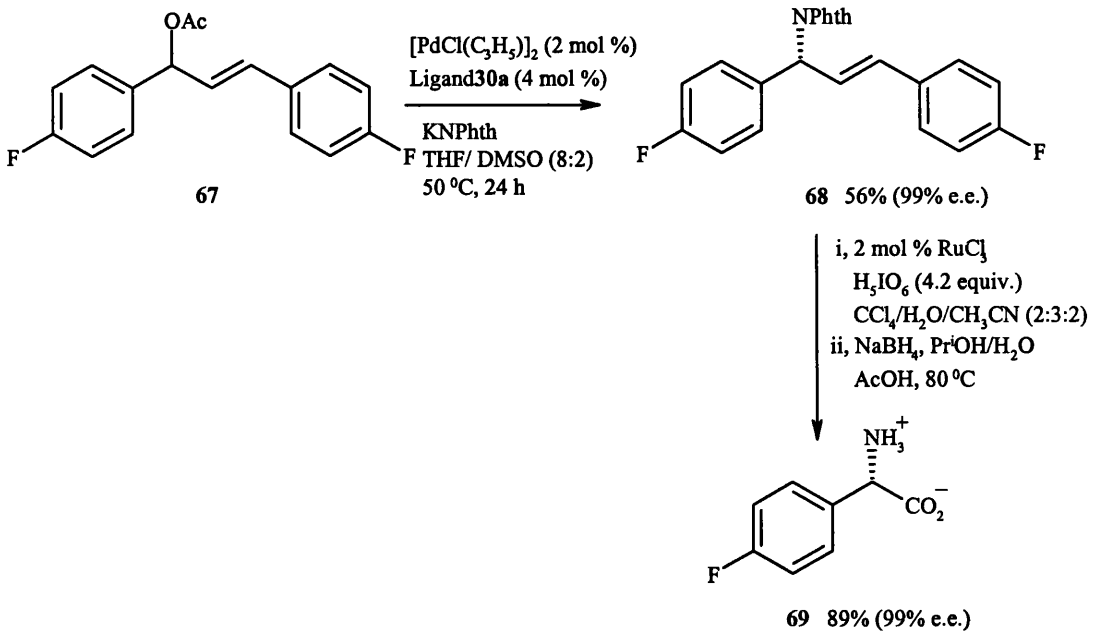


65 **66**

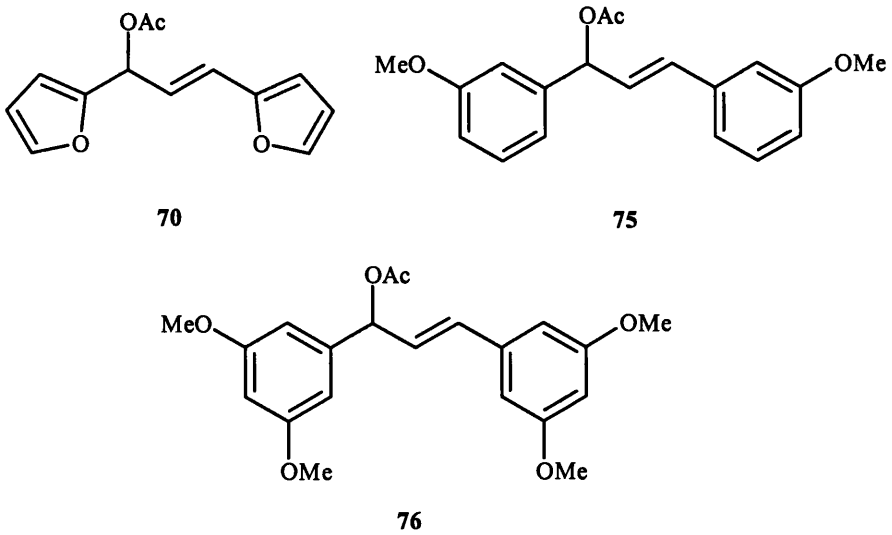
The asymmetric runs of the reactions were not pursued, even though the N-substituted products were formed, because of the low chemical yields experienced in the initial racemic reactions. The disappointing results with the above nitrogen nucleophiles led us to return to the highly selective and high yielding phthalimide nucleophile.

2.4 Aromatic substrates in palladium catalysed allylic substitution

It has been shown by this group[84] that allylic amine products from the test bed substrate, 1,3-diphenylprop-2-enyl acetate **20**, can afford highly enantiomerically enriched amino acids through selective oxidations. The amino acids accessible from the allylic amine product by oxidative cleavage however, are limited to glycine or glutamic acid derivatives. In earlier publications, Williams *et al* [84] showed that the fluoro analogue of 1,3-diphenylprop-2-enyl acetate **67** affords the substitution product **68** in the palladium catalysed alkylation with an impressive e.e. of 99%, which was successfully carried through to the glycine analogue **69**.



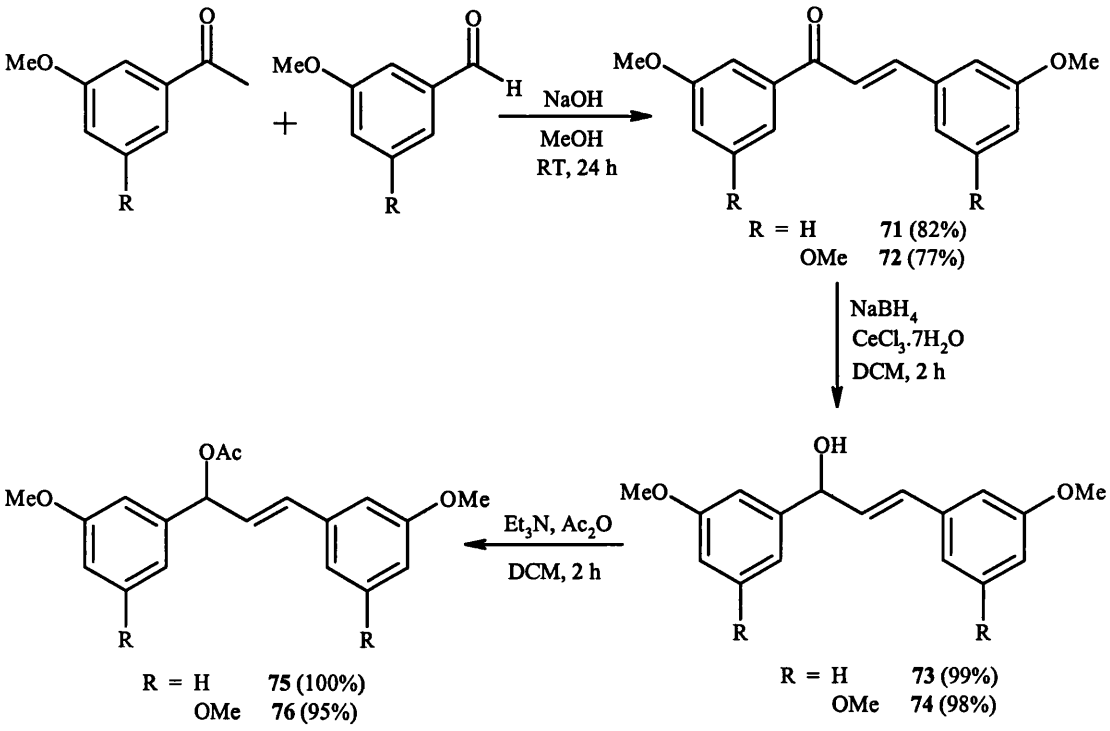
We wanted to take the methodology further by preparing allylic amine substitution products from the allylic acetates **70, 75** and **76**.



The position of the methoxy group in the allylic acetate is important to the reactivity of the substrate in the palladium catalysed allylic substitution reaction. Previously in the research group it was demonstrated that nucleophilic substitution did not prevail when the methoxy group was in the *ortho* or the *para* position.[88] It

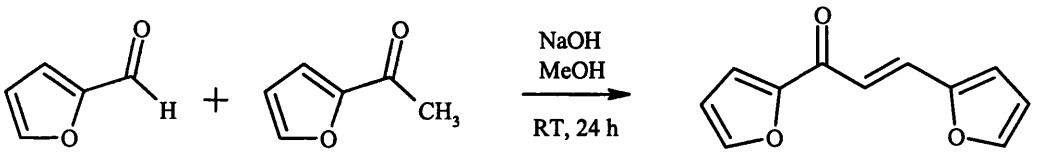
is postulated that when the substituent in this in either of these positions, the resonance structures may affect the stability of the π-allyl intermediate, reducing the electrophilic nature of the complex and preventing the nucleophile from displacing the palladium. Substituents in the *meta* position however, localise the resonance to the aromatic rings and should not influence the π-allylic complex.

The base catalysed Claisen-Schmidt Aldol reaction[89] of 3-methoxyacetophenone and 3-anisaldehyde gives the α-β-unsaturated ketone **71** as the sole product. Analysis of the ^{1}H NMR data indicated the presence of olefin signals at δ6.95 and δ7.11 and the compound also gave a peak in the mass spectrum of MH^+ 269.1 to confirm the condensation of the substrates. Reduction of the unsaturated ketone to the allylic alcohol **73** was carried out under Luche reduction conditions[90] with sodium borohydride and cerium chloride heptahydrate.



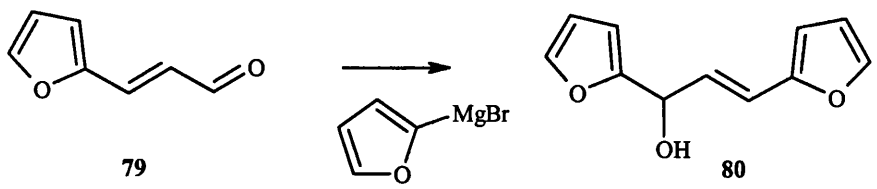
The appearance of an OH singlet at δ1.61 and a triplet at δ5.04 in the ^{1}H NMR spectrum together with the disappearance of the C=O stretch in the infrared allowed the acetylation to be carried out. The alcohol **73** was acetylated using the standard conditions of triethylamine and acetic anhydride with dimethyl aminopyridine to afford the allylic acetate **75.** Determination of an acetate group was carried out by ^{1}H NMR with the appearance of a methyl singlet at δ2.13 and a C=O stretch in the infrared at 1716 cm^{-1}. The dimethoxy allylic acetate **76** was prepared in a similar manner. Both allylic acetates, **75** and **76,** were stored below 0 °C to slow down the degradation to the allyic alcohol, which occurs in a couple of days at room temperature.

The base catalysed Claisen-Schmidt condensation was also successful in the preparation of the furyl derivative **77.** However, the Luche reduction using sodium borohydride and cerium chloride heptahydrate gave a black tar of a multitude of products.



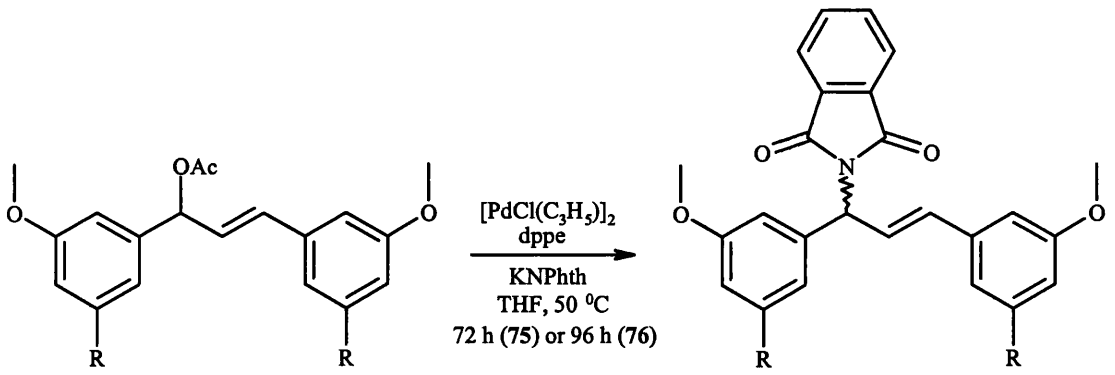
77

The attempted formation of the allylic alcohol **80** by addition of the Grignard reagent **78** to the unsaturated ketone **79** also encountered problems.[91] A possible explanation is that the expulsion of the newly formed hydroxy group occurs because of strong resonance stabilisation in the resulting conjugated aromatic system.



79 **78** **80**

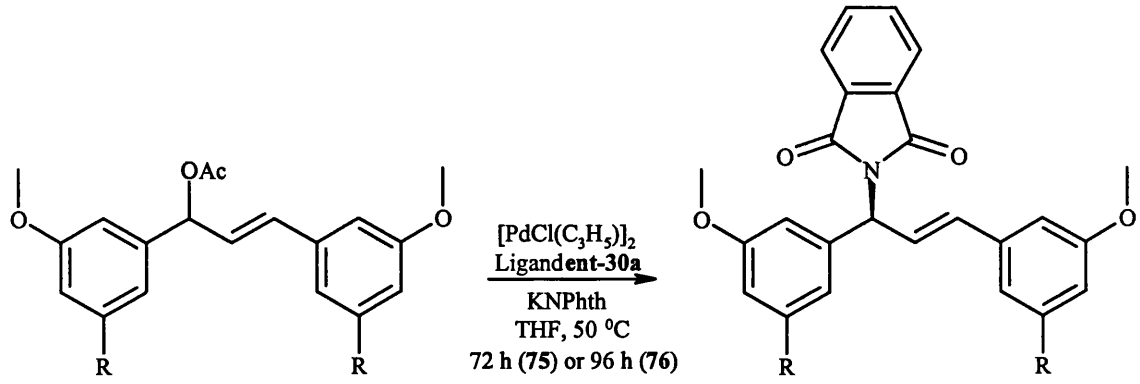
The palladium catalysed allylic substitution of allylic acetates **75** and **76** using the prochiral catalyst, palladium allyl chloride dimer / bisdiphenylphosphinoethane, gives the substitution products **81** and **82** respectively. The introduction of the phthalimide moiety was denoted in the ^{1}H NMR by the loss of the acetate methyl singlet at δ2.13, and the appearance of two multiplets, low field at δ7.77 and δ7.83, representing the phthalimide protons. Compound **81** was confirmed by the characteristic stretch of the phthalimide imide at 1771 and 1711 cm^{-1} in the infrared spectrum and a high resolution mass spectrum of M^+ 399.1469. It is noted that the introduction of methoxy groups on the phenyl rings slowed the rate of the allylic substitution. The reaction with substrate **75** took 72 hours for complete consumption and acetate **76,** 96 hours (*c.a.* 1,3-diphenylprop-2-ene acetate **20**, 48 hours).



R = H **75**
= OMe **76**

R = H **81** 69%
= OMe **82** 40%

The asymmetric reaction with the methoxyphenyl allylic acetates proceeded with higher chemical yields than the racemic versions, and very good enantiomeric excesses were also observed. Both the (*R*) and the (*S*) enantiomers have been prepared using the corresponding (*R*) and (*S*) oxazoline ligands **30a** and **ent-30a**. The enantiomeric excesses for both allylic amines were calculated by HPLC analysis (chiracel OD chiral column) with **81** giving 92% e.e. and amine **82** giving 93% e.e..



R = H **75**
= OMe **76**

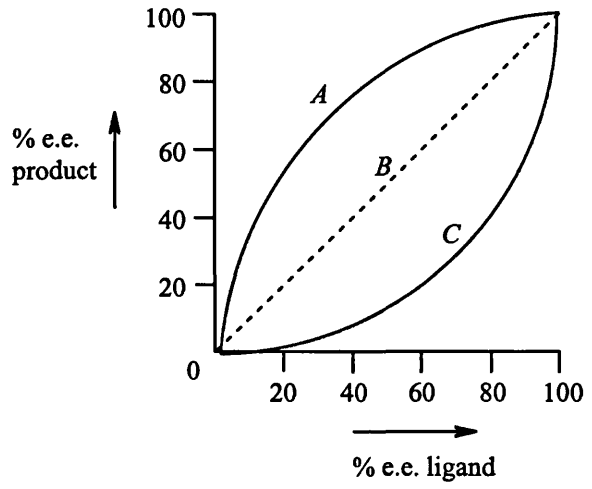
R = H **81** 88% (92% e.e.)
= OMe **82** 65% (93% e.e.)

2.5 Non-linear effects in palladium and platinum catalysed allylic substitution reactions

The asymmetric ligand **30a** in the palladium catalysed allylic substitution determines the stereochemistry of the product by the stereochemistry at the stereogenic centre of the oxazoline unit. The use of enantiomerically pure ligands can generate excellent selectivity in the reaction. However, is the enantiomeric excess of the substitution product a direct correlation from the enantiomeric excess of the ligand? If not, can substitution products be formed at high e.e. while using oxazoline ligand **30a** at a lower e.e.?

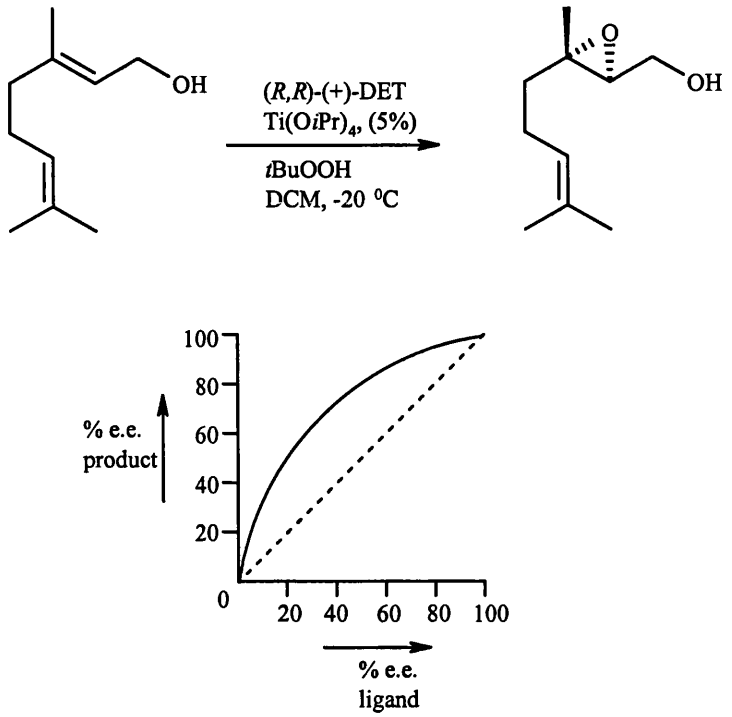
If the relationship between the e.e. of the ligand and the e.e. of the product deviates from linearity, a non-linear effect is observed.[92] Scheme 2.4 illustrates the relationship between the e.e. of ligand and the e.e. of product. Line A shows a positive non-linear effect where the observed e.e. of the product is higher than a linear relationship (line B). Line C shows a negative non-linear relationship where the observed e.e. is lower than a linear relationship.

Scheme 2.4



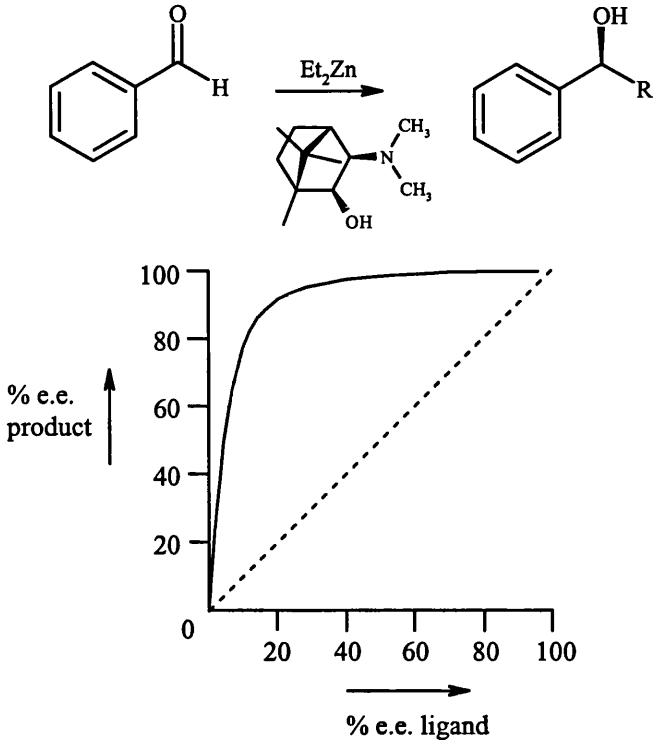
There are many examples in the literature of non-linear effects in asymmetric catalyses.[93] A positive non-linear effect is observed in the Sharpless epoxidation of geraniol with (*R,R*)-(+)-diethyl tartrate.[94] The e.e. of the epoxide product when plotted as a function of the e.e. of (+) DET and was found to be greater than the expected linear result (Scheme 2.5).

Scheme 2.5

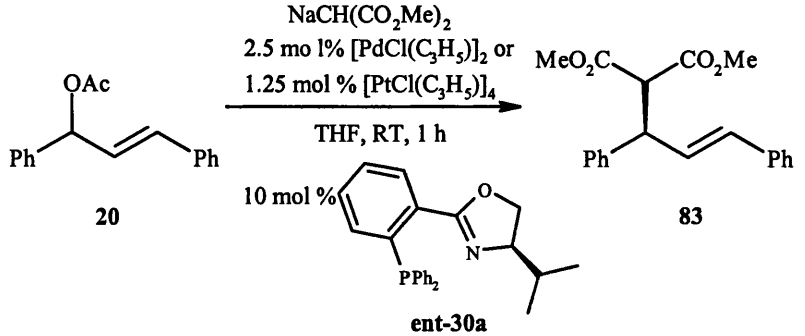


A strong positive non-linear effect is also seen with organozinc additions to aldehydes. Noyori *et al* published results from mechanistic studies of organozinc additions to aldehydes catalysed by (-)-3-*exo*-(dimethylamino)*iso*borneol (DIAB).[95] The maximum enantioselectivity of the reaction is reached at very low e.e. of the catalyst (Scheme 2.6). The positive non-linear effects here are explained by the formation of dimeric species in solution. The heterochiral dimer (which retains the minor enantiomer) is the more stable complex (and the less reactive species), leaving the homochiral active dimer to catalyse the reaction. These types of positive non-linear effects have been named 'asymmetric amplification'.

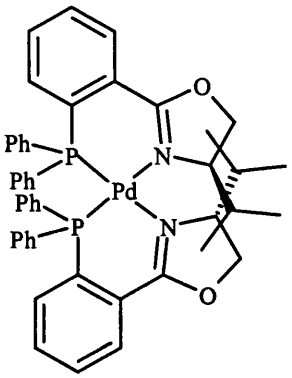
Scheme 2.6



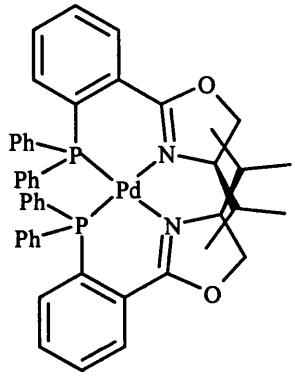
Non-linear effects for the asymmetric palladium and platinum catalysed allylic substitution reaction were explored using the model system of 1,3-diphenylprop-2-enyl acetate **20**, giving the substitution product **83** when reacted with the sodium dimethyl malonate as nucleophile. The palladium catalyst was generated from the palladium allyl chloride dimer and phosphinooxazoline **ent-30a**; the platinum catalyst from platinum allyl chloride tetramer and phosphinooxazoline **ent-30a**.



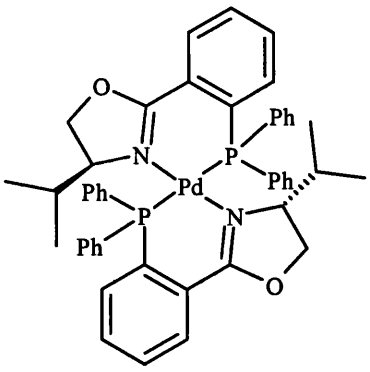
For the palladium catalyst is it assumed that in solution two molecules of the ligand will bind to the free palladium before the substrate is added. The stereochemistry of this complex may reside as four possible forms **84-87**. To obtain a non-linear effect the heterodimers, **85** and **86,** must be sufficiently more stable than the homodimers, **84** and **87**, in solution, to allow the observed e.e. of the catalyst to be higher than the actual e.e. of the ligand.



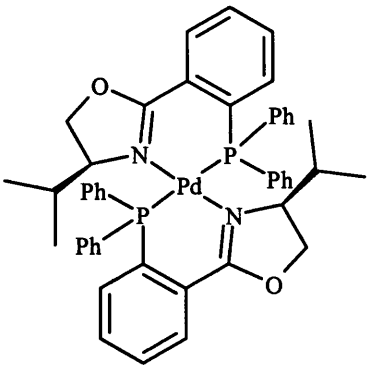
84



85



86



87

For the palladium reactions 1.25 mol % $[PdCl(C_3H_5)]_2$ is pre-stirred with 5 mol % of ligand **ent-30a** in THF at room temperature for 10 min (1.25mol % of $[PdCl(C_3H_5)]_2$ equates to 2.5 mol % of palladium species). The enantiomeric value of the ligand is started at 100% with enantiomerically pure (*R*) isomer (entry 1),

and with subsequent runs decreased by 20% down to racemic ligand. The sodium salt of dimethyl malonate is cannulared into the reaction vessel and the mixture stirred for 20 min or until complete consumption of the allylic acetate **20**. HPLC analysis using an OD chiracel column identified the enantiomeric excesses of the substitution products. The results are shown in Table 2.2 and Figure 2.2.

Table 2.2 Enantioselectivity (%) of dimethyl 1,3-diphenylprop-2-enyl malonate **83** with % e.e. of ligand **ent-30a** in the palladium catalysed allylic substitution

Entry	Ligand ent-30a e.e. (%)	Product 83 e.e. (%)
1	100	96
2	80	74
3	60	59
4	40	40
5	20	19
6	0	3

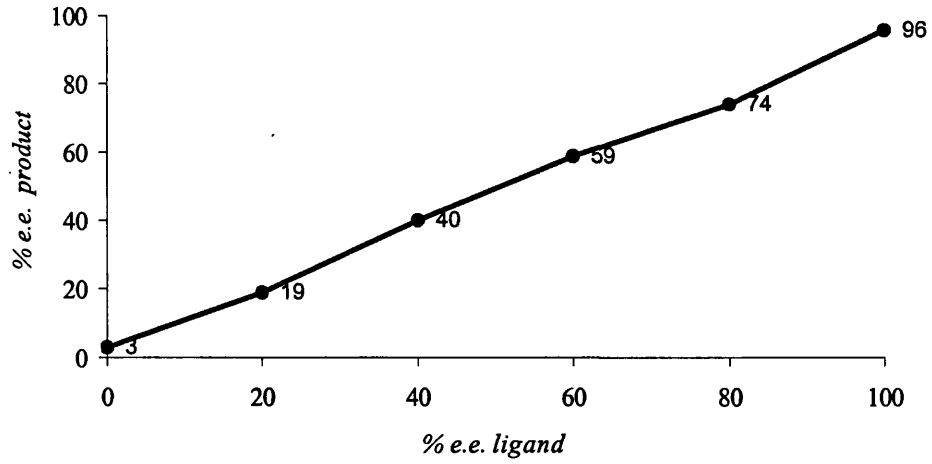
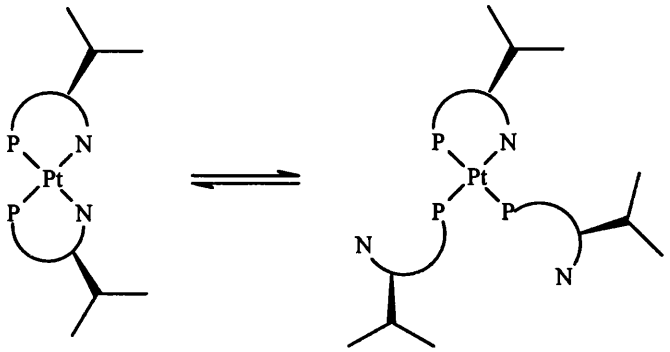


Figure 2.2 Relationship of % e.e. of dimethyl 1,3-diphenylprop-2-enylmalonate **83** against % e.e. ligand **ent-30a** with the palladium catalyst

The platinum complex is also believed to adopt similar type dimer arrangements in solution. However, in the case of platinum, there is evidence that the metal does not bind to the mixed donor ligand **ent-30a** as strongly as palladium in solution, and the catalytic complex **88** may exist in equilibrium with complex **89**.[96] When the ligand binds mono-dentately, as in structure **89**, the enantioselection is assumed lost in the reaction explaining the observed drop in e.e. for the platinum reactions (compared to the palladium reactions). The enantioselectivities of the substitution product with platinum and ligand **ent-30a** are shown in Table 2.3 and Figure 2.3.



88 **89**

Table 2.3 Enantioselectivity (%) of dimethyl 1,3-diphenylprop-2-enyl malonate **83** with % e.e. of ligand **ent-30a** in the platinum catalysed allylic substitution.

Entry	Ligand ent-30a e.e. (%)	Product 83 e.e. (%)
1	100	66
2	80	51
3	60	44
4	50	37
5	40	27
6	20	15
7	0	3

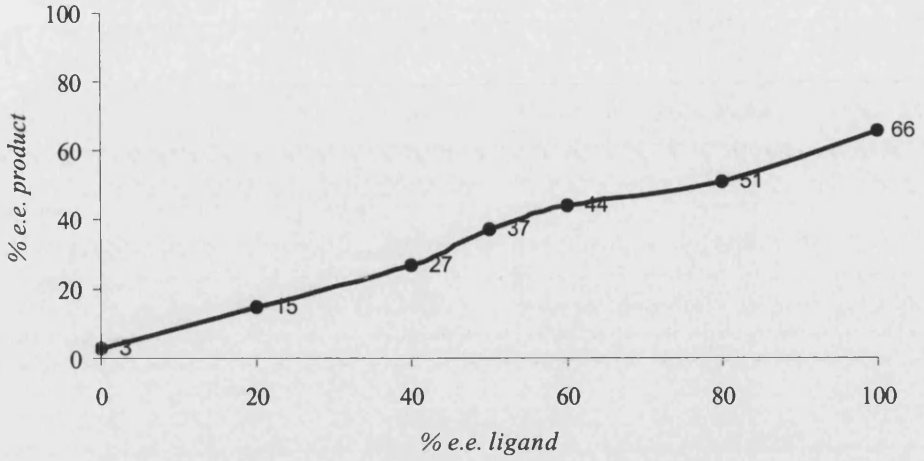
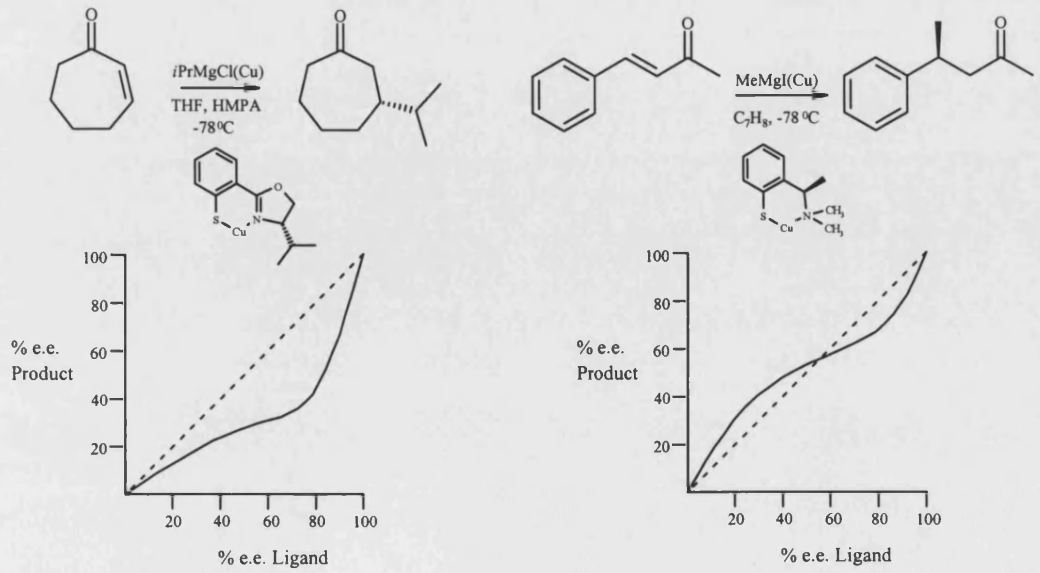


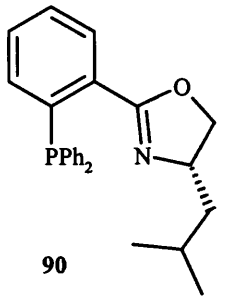
Figure 2.3 Relationship of % e.e. of dimethyl 1,3-diphenylprop-2-enyl malonate **83** against % e.e. ligand **ent-30a** with the platinum catalyst

The results indicate a linear relationship between the e.e. of the ligand and the e.e. of the product. There is a slight positive effect from linearity around the mid e.e. % of ligand. This slight deviation from linearity has been accounted for by experimental error, however, it must be noted that multishaped and negative non-linear effects have been observed with oxazoline ligands in copper catalysed 1,4-additions (Scheme 2.7).[97, 98]

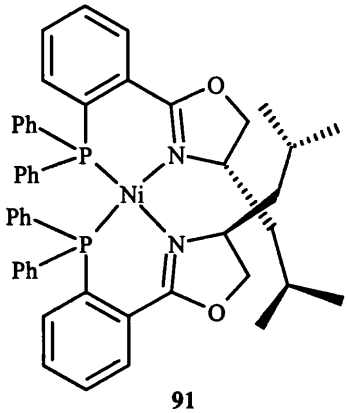
Scheme 2.7



A linear relationship for the palladium and platinum catalysed allylic substitution reaction with the phosphinooxazoline ligand **ent-30a** would correlate with recent work published by Lloyd-Jones.[99] Using nickel centred complexes Lloyd-Jones has shown that oxazoline ligand **90** binds as a dimer where the homochiral complex **91** is the preferred arrangement. The best fit is seen to be where the π-accepting phosphorus centres are both *trans* to the donating nitrogen centres (*c.a.* **84** and **85** in our case).



90



91

Comparing the heterochiral and homochiral assembly, Lloyd-Jones has shown that in the heterochiral complex there will be at least two sites of steric clash. One between the two psuedo-equatorial phenyl rings, and one between the two *iso*butyl chains. The homochiral complex has a 'clash free' staggered conformation. If these arguments are employed with the palladium and platinum/ligand **ent-30a** complexes we would observe ratios of homochiral (*R*) and (*S*) complexes both as active catalysts ensuing a linear relation of ligand e.e. to product e.e..

In the non-linear effect experiments the reaction rate of the runs using 100% e.e. ligand with the palladium and platinum catalysts were recorded. In the palladium

catalysed substitutions the enantiomeric excess of the substitution product started at 93% e.e. and remained constant throughout the course of the reaction.

Table 2.4 The % e.e. of substrate **20** and product **83** over time with the $[PdCl(C_3H_5)]_2$/ ligand **ent-30a** as catalyst.

Time (min.)	Substrate e.e. (%)	Product e.e. (%)	Conversion (%)
1	20	93	52
3	28	93	69
5	40	93	82
7	50	93	89
11	61	93	95
19	65	93	99

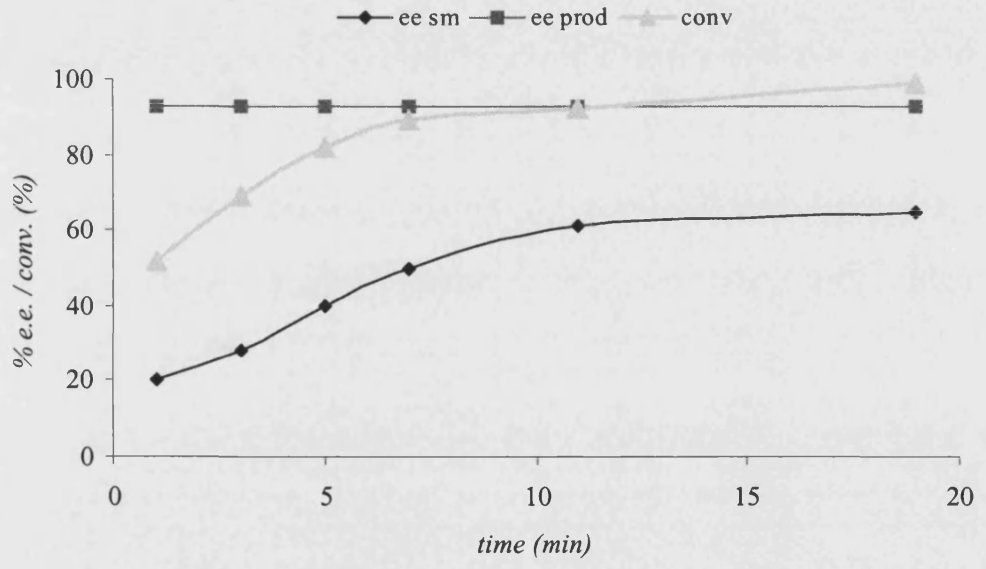


Figure 2.4 Graph of conversion (%) and e.e. (%) of substrate **20** and product **83** with time using $[PdCl(C_3H_5)]_2$/ ligand **ent-30a** catalyst.

Interestingly, however, the enantiomeric excess of the racemic allyl acetate being consumed developed an e.e. as the reaction progressed, Figure 2.4 (Table 2.4). It is assumed that while the reaction proceeds through a common π-allyl intermediate, the catalyst has an affinity for one allyl acetate enantiomer, even though both are converted to the same enantiomer in the substitution product.

For the platinum catalysed reactions the reduced activity of the catalyst did not see conversions progress past 50%. The profiles in Figure 2.5 (and Table 2.5) indicate the reaction stops after approximately two hours, while the initial data points suggest that the platinum catalyst has similar reaction kinetics to the palladium catalyst, showing higher affinity for one enantiomer of the allyl acetate.

Table 2.5 The % e.e. of substrate **20** and product **83** over time with the $[PtCl(C_3H_5)]_4$/ ligand **ent-30a** as catalyst.

Time (h)	Substrate e.e. (%)	Product e.e. (%)	Conversion (%)
0.25	4	55	25
0.5	7	58	42
1	10	57	52
1.5	11	56	52
2	10	56	51
3	11	56	51
5	11	56	52
6	17	56	51
9	12	56	51
19	15	57	51

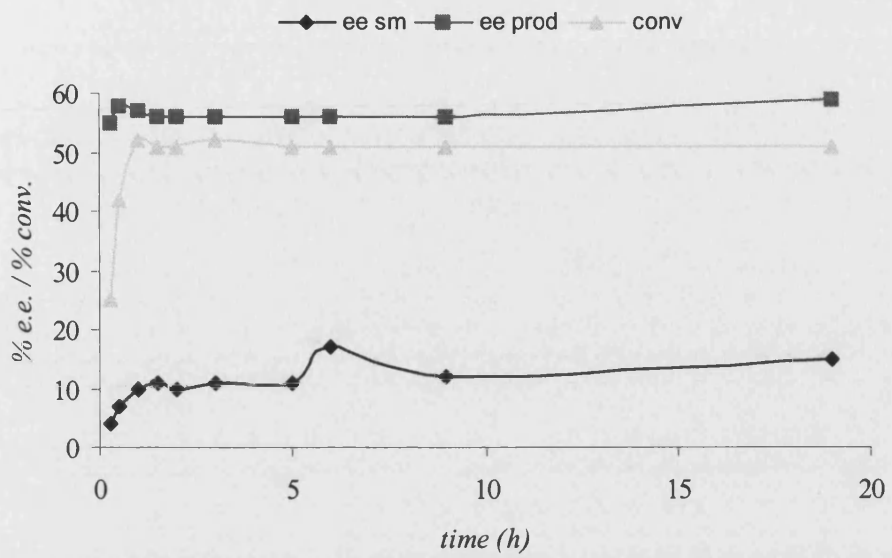


Figure 2.5 Graph of conversion (%) and e.e. (%) of substrate **20** and product **83** with time using $[PtCl(C_3H_5)]_4$/ ligand **ent-30a** catalyst.

2.6 Conclusion

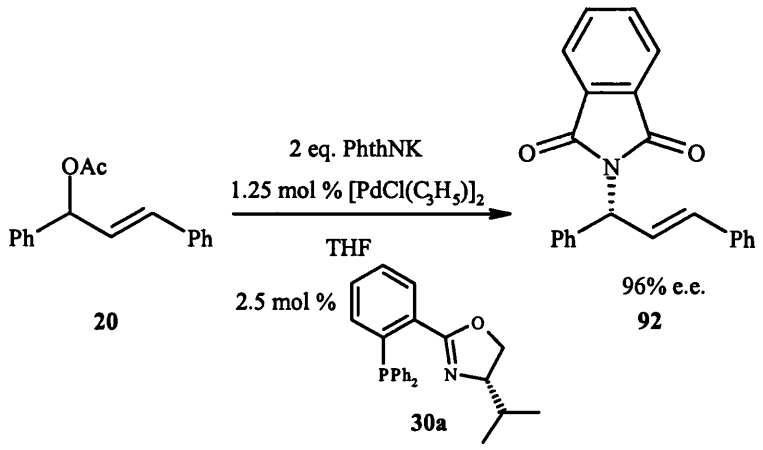
The nitrogen nucleophiles tested in the palladium catalysed allylic substitution reaction with the phosphinooxazoline **30a** as ligand, proved less successful in terms of the enantioselectivity and yield of the reaction than the nucleophile potassium phthalimide. The palladium catalysed allylic substitution using potassium phthalimide as the nucleophile, with bis methoxyphenyl and bis dimethoxy phenyl allylic acetate substrates showed very high enantioselectivities (92-93% e.e.) and good yields (65-88%). The preparation of the (*R*) and the (*S*) enantiomers of phosphinooxazoline ligand **30a** (**ent-30a**), showed that a linear relationship between the e.e. of ligand and e.e. of product is observed in the palladium and platinum catalysed allylic substitution reaction.

Chapter 3

3 Enantiomerically Pure Nucleophiles in Palladium Catalysed Allylic Substitution

3.1 Introduction

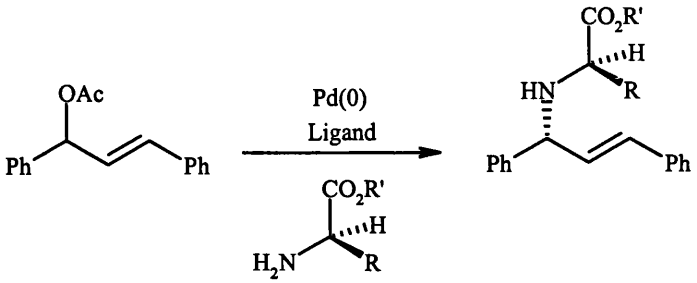
The use of nitrogen nucleophiles in the palladium catalysed allylic substitution reaction is well documented (Chapter 1). Many variants have been utilised to incorporate the amine functionality into molecules. When enantioselective control is desired, bidentate phosphine ligands have been replaced by asymmetric ligands such as the phosphooxazoline ligand **30a,** giving excellent selectivity with diphenyl substrates such as allyl acetate **20,** affording allylic amine **92** in a good yield of 91% and up to 96% e.e..



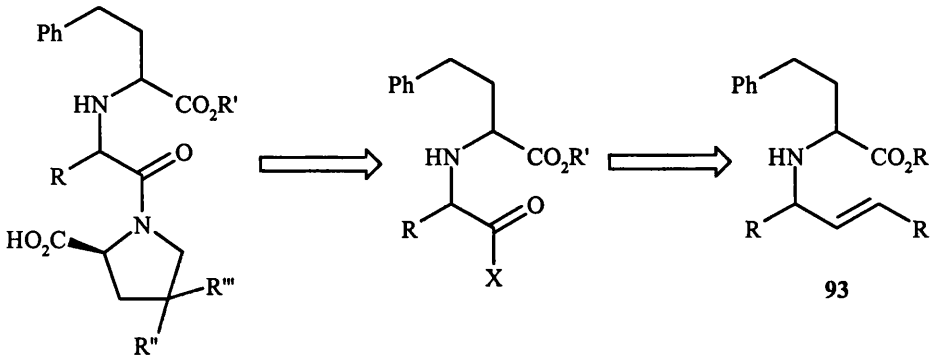
Our interest was aroused by the idea of using an enantiomerically pure nucleophile in the palladium catalysed alkylation with a prochiral catalyst, to induce stereocontrol in the allylic amine product. To investigate this hypothesis amino acid esters were chosen as a template for the enantiomerically pure nucleophile in the substitution of allylic acetate **20** (Scheme 3.1). Amino acid esters would seem a reasonable choice, as the two different variables giving the

nucleophile its chirality (the ester and the amino acid side chain) could be manipulated easily.

Scheme 3.1



The use of amino esters as nucleophiles in allylic alkylations can present a synthetically useful class of compounds. Many biologically interesting structures can be accessed from these allylic amine products.[100] For example, the clinically proven Angiotensin Converting Enzyme inhibitors (ACE inhibitors) enalapril **94**[101] and lisinopril **95**[102] can be traced back reterosynthetically to the palladium catalysed substitution product **93**, from the alkylation of pent-2-enyl acetate with homophenylalanine.

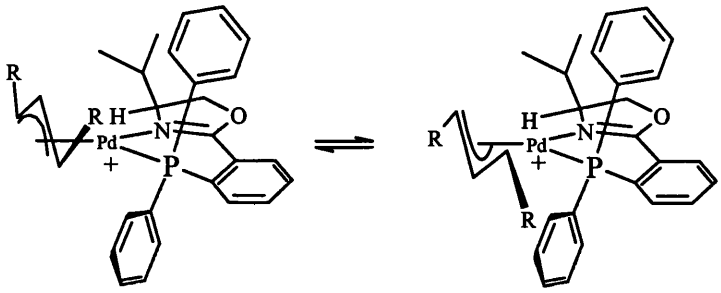


94 R = CH_3
95 R = $(CH_2)_4NH_2$

The enantiomeric control provided by ligand **30a** in the palladium catalysed allylic substitution reaction, as discussed in Chapters 1 and 2, arises from the

ligand's design to favour the 'W' orientation (Scheme 3.2) for nucleophilic attack. In the allylic substitution reaction with a prochiral palladium catalyst, such as $[PdCl(C_3H_5)]_2$/bisdiphenylphosphinoethane, the 'M' and the 'W' orientations are equally favoured and no selectivity is observed in the substitution product.

Scheme 3.2



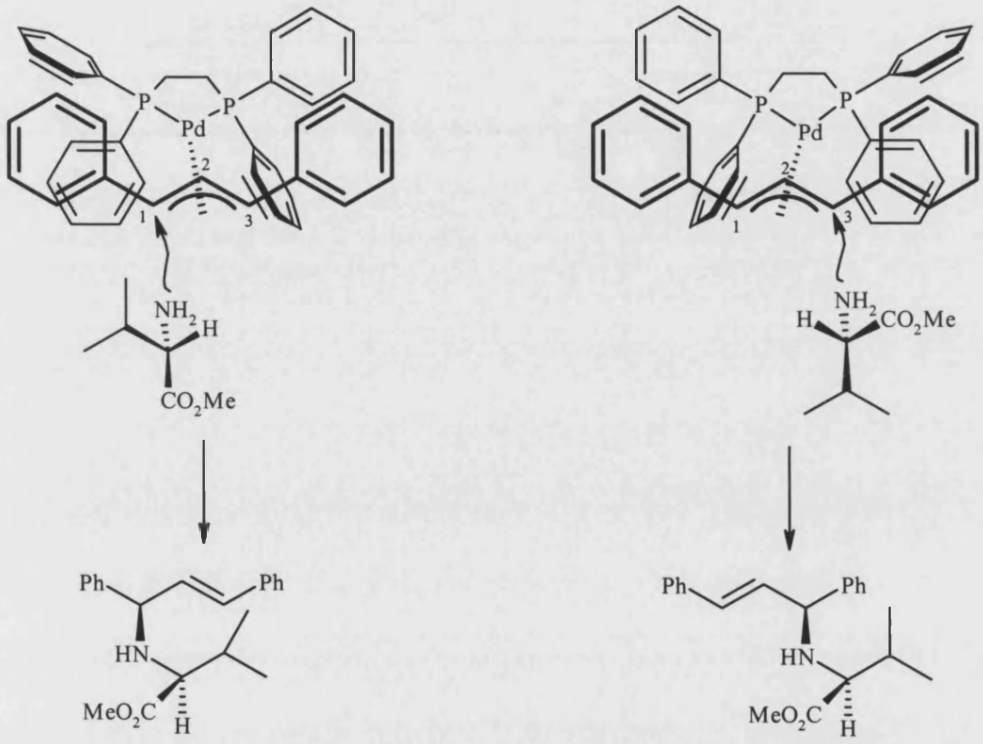
'W' Orientation 'M' Orientation

If we consider nucleophilic attack of an enantiomerically pure amino ester at a prochiral catalytic complex, the chiral nature of the molecule will produce different interactions with the π-allyl intermediate on approach to either, the C1 or the C3 termini of the 'W' orientation (or the 'M' orientation). If nucleophilic attack occurs on the π-allyl system, with for example, the methyl ester of *L*-valine, we can assume that the nucleophile will approach the site with the least steric interaction. So the smallest group, i.e. hydrogen, will occupy the most crowded area. Scheme 3.3 illustrates the model that we have proposed.

At the catalytic intermediate it is assumed that the phosphorus phenyl rings adopt a staggered orientation, effectively making the space around C3 very hindered while favouring attack at C1 (alternatively, if the space around C1 is very hindered, attack will be favoured at C3). Nucleophilic attack at C1 with the

enantiomerically pure *L*-amino ester will proceed with the hydrogen of the nucleophile approaching closest to C3 and the ester functionality facing away from the complex. Conversely, when attacking C3 in the 'W' orientation (or C1 in the 'M' orientation) the isopropyl group will be facing away from the complex.

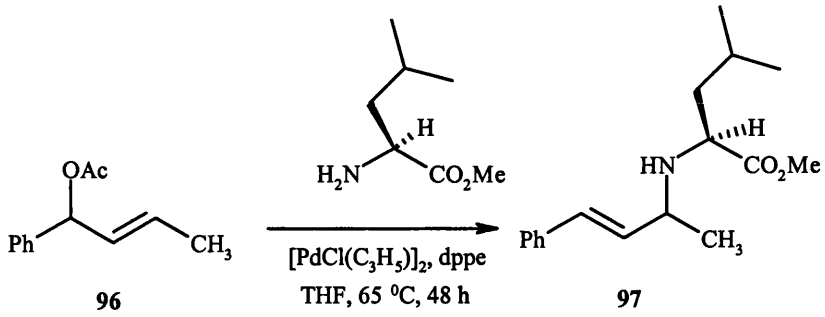
Scheme 3.3



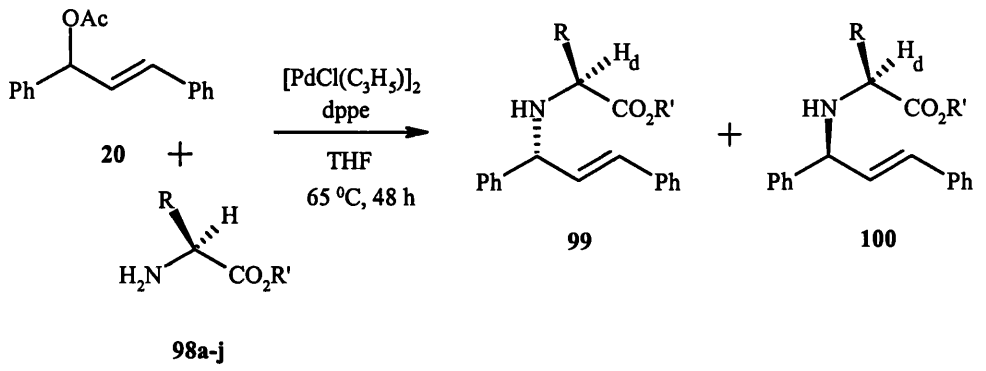
3.2 Enatiomerically pure nucleophiles with prochiral catalysts

L-Amino esters **98a-j** were reacted with 1,3-diphenylprop-2-enyl acetate **20** with the prochiral catalyst, palladium allyl chloride dimer/ bisdiphenylphosphinoethane, in THF at 65 ^{0}C for 48 hours. To allow an accurate determination of the level of selectivity given by the nucleophile, it is important to use a symmetrical allylic substrate. Using an unsymmetrical substrate, such as 1-phenylbut-2-enyl acetate **96**, the methyl ester of *L*-leucine forms the allylic

amine **97** with attack occurring at the less hindered termini. It is known that with soft nucleophiles (amines for example) the preferred site of attack is at the less hindered termini; hard nucleophiles attack at the more substituted termini through initial coordination to the metal center.[5]



Enantiomerically pure *L*-amino esters were chosen for the reasons explained earlier (page 45) so only two diastereomeric products, **99** and **100**, are produced in the transformation. This enables the e.e. at the newly formed stereogenic centre to be determined by the diastereomeric ratio in the reaction mixture. The two diastereomeric products were found to be inseparable by silica gel flash column chromatography and were isolated as a viscous oil. The diastereomeric ratio of the mixture was measured from the ^{1}H NMR data, by the relative intensities of either proton H_d or the methyl singlet of the ester.



The selection of the amino esters **98a-j** allows us to determine which groups affect selectivity in the allylic substitution. The size of both the ester group and the side chain were varied for this reason.

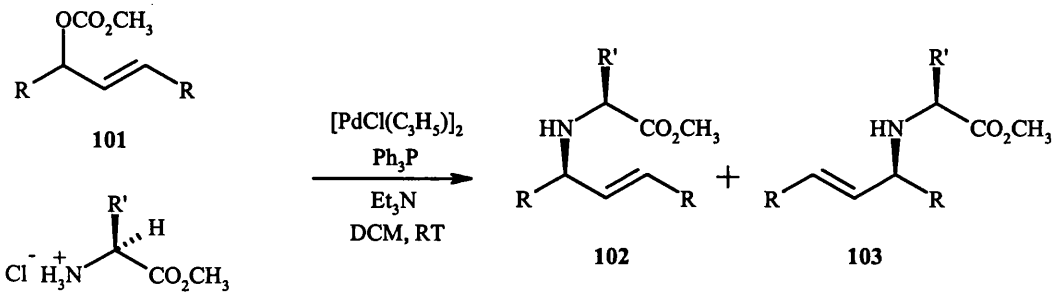
Excellent diastereocontrol was observed with the methyl esters (70-20% d.e.) and it was plausible to presume that increasing the size of the ester would also increase the diastereoselectivity. However, the experiments using ethyl and *tert*-butyl esters suggested a different explanation (Table 3.1). The opposite affect was seen and the trend was, the larger the ester group, the poorer the selectivity. The amino acid side chain of the nucleophile would appear to be less influential for diastereoselectivity, with only a tentative suggestion that the bulkier the functionality at the side chain the poorer the d.e..

Table 3.1 Diastereoselectivity in the palladium catalysed substitution of allylic actetate **20** with enantiomerically pure amino esters **98**

Amino Ester 98	R	R'	Yield (%)	Diastereomer Ratio (99:100)
a	^{i}Bu	Me	69	85:15
b	^{i}Pr	Me	72	80:20
c	Ph	Me	68	73:27
d	CH_2Ph	Me	74	60:40
e	Me	Et	56	61:39
f	^{i}Bu	Et	70	65:35
g	^{i}Pr	Et	70	60:40
h	Ph	Et	26	56:44
i	Me	^{t}Bu	45	58:42
j	^{i}Bu	^{t}Bu	79	57:43

In applying our proposed model to the results from the allylic substitutions in Table 3.1 we may propose that: 1) the methyl esters, which offer the best d.e., are small enough to fit into a low energy pathway avoiding major steric interactions when approaching the allylic termini. 2) Increasing the size of the ester moiety disfavours the nucleophile from entering into this reaction pocket due to increased steric constraints, therefore, allowing less selective reactions to occur.

Concurrent research conducted independently by Trost *et al* supports our results. Contemporaneous with the publication of our preliminary findings,[103] Trost demonstrated that the palladium catalysed allylic substitution, of allylic acetate **101** using a palladium/ triphenylphosphine catalyst and the methyl esters of phenylalanine and serine, gave d.e.'s of 50% for the substitution products **102** and **103**.[104]

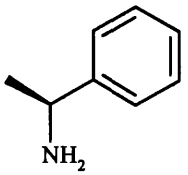


R' = CH_2Ph, CH_2OH
R = CH_3, CH_2CH_3

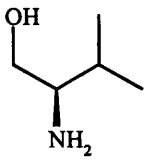
All the results show that enantiomerically pure chiral amine nucleophiles can be utilised in palladium catalysed allylic substitution reactions to give diastereocontrol in the substitution product. We have observed that the smaller the ester group, the better the diastereoselectivity. However the question arises; must an ester group be present in the chiral nucleophile to give the selectivity? Is the diastereoselectivity observed in the reaction, from the steric properties of the

ester, the electronic properties of the ester, or, does the ester moiety hydrogen bond prior to attack?

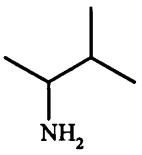
To investigate these points, enantiomerically pure α-methyl benzylamine **98l**, *L*-valinol **98m** and the chiral 1,2-dimethylpropylamine **98n** were used as nucleophiles with the $[PdCl(C_3H_5)]_2$/dppe catalyst in the substitution of allyl acetate **20**. The results are displayed in Table 3.2.



98l



98m



98n

The inability of the ester group replacements, methyl and hydroxyl in nucleophiles **98l-n**, to generate diastereoselectivity suggests that the ester group is not merely a size factor enforcing the diastereocontrol.

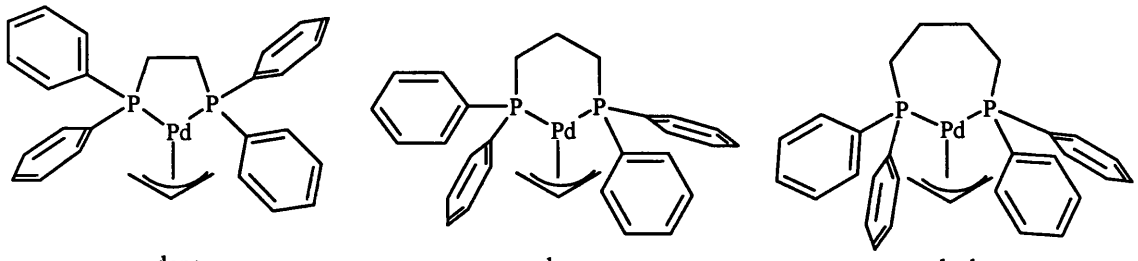
Table 3.2 Comparison of diastereomeric ratios of products **99** and **100** for chiral amines and chiral amino esters.

Nucleophile	Yield (%)	Diastereomer Ratio (99:100)
98l	89	53:47
98m	64	50:50
98n	85	53:47
98b	72	80:20
98c	68	73:27

With the ester functionality displaying its importance in the make up of the chiral nucleophile, the reaction conditions with amino esters were probed for improvement.

The first area of the reaction examined was the ligand. If you imagined the diphosphine ligand complexed to the palladium in the π-allyl intermediate, the orientation of the phenyl rings attached to the phosphorus atoms are controlled by the bridging chain between the two phosphorus atoms. Increasing the length of the chain between the phosphorus atoms will affect the position of the phenyl rings, possibly changing the interactions with incoming nucleophiles (Scheme 3.4).

Scheme 3.4



dppe dppp dppb

Samantha Regini† carried out reactions in the hope of optimising the d.e. of the reaction. To ascertain whether different ligands affected the d.e. of the substitution product, allyl acetate **20** was reacted with *L*-leucine methyl ester **98a** using palladium chloride allyl dimer and bidentate diphosphine ligands as the catalyst, under conditions previously used in the formation of products **99a** and

† Samantha Regini was a Chemistry MSc. student from Pavia University, Italy on a six month transfer at the University of Bath.

100a. Table 3.3 lists the diastereomeric ratio and chemical yield of the transformations.

Table 3.3 Diastereomeric ratios and chemical yields of compound **99a:100a** with phosphine ligands

Ligand	Yield (%)	Diastereomeric ratio (99a:100a)
$Ph_2PCH_2CH_2PPh_2$	69	69:31
$Ph_2PCH_2CH_2CH_2PPh2$	51	64:36
$Ph_2PCH_2CH_2CH_2CH_2PPh2$	67	65:35
2 x PPh_3	81	63:37

The anticipated change in orientation of the rings would seem to not influence the d.e or the yield of the reaction. The monodentate triphenylphosphine ligand did see a marginal increase in the chemical yield of the product with comparable d.e. to the bidentate ligands.

The influence of the type of solvent appeared to give greater changes to the d.e. of the product. The results in Table 3.4 illustrate that aprotic solvents such as, THF and diethyl ether, give the best chemical and diastereoselective results. Non-polar solvents, such as toluene, give good diastereoselectivity but with lower chemical yield, and DCM gave no reaction at all. DMF gave a diastereochemical result comparable with the ratios from THF or diethyl ether as solvent, but the low yields, possibly resulting from loss of product in the extractive workup, removes this polar solvent from being the first choice.

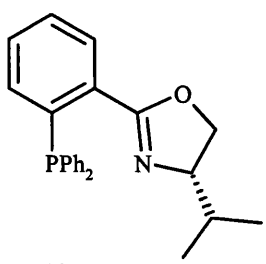
Table 3.4 Diastereoselectivities of compounds **99a:100a** with different solvents

Solvent	Yield (%)	Diastereomeric ratio (99a:100a)
THF	69	69:31
Et_2O	74	69:31
Toluene	42	65:35
DCM	0	0
DMF	17	56:44

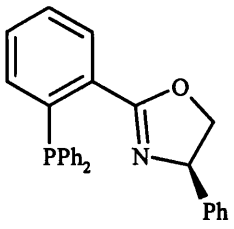
3.3 Enantiomerically Pure Ligands

The substitution reaction with enantiomerically pure amino esters and prochiral catalysts demonstrated that a certain degree of stereocontrol can be achieved using the appropriate nucleophiles. It is therefore logical to postulate that, a correct combination of directing enantiomerically pure chiral nucleophile and enantiomerically pure ligand will result in a matched pairing, yielding allylic amines with enhanced diastereomeric excesses.

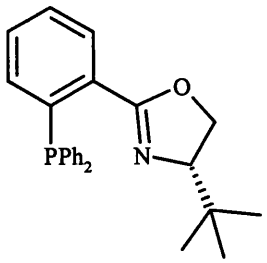
For the transformation of the allyl acetate **20** to the amine diastereoisomers **99/100** and **ent-99/ent-100**, the enantiomerically pure *L*-amino esters **98a-d** and enantiomerically pure *D*-amino esters **ent-98a-d** were combined with the palladium catalyst, $[PdCl(C_3H_5)]_2$/ ligands **30a-c**. Four substitution products are possible from the combinations (their relationship, in terms of diastereoisomers and enantiomers are shown in Scheme 3.5). However, by using the *D*- and the *L*-amino esters in separate reactions only two diastereoisomers are observed in each reaction.



30a

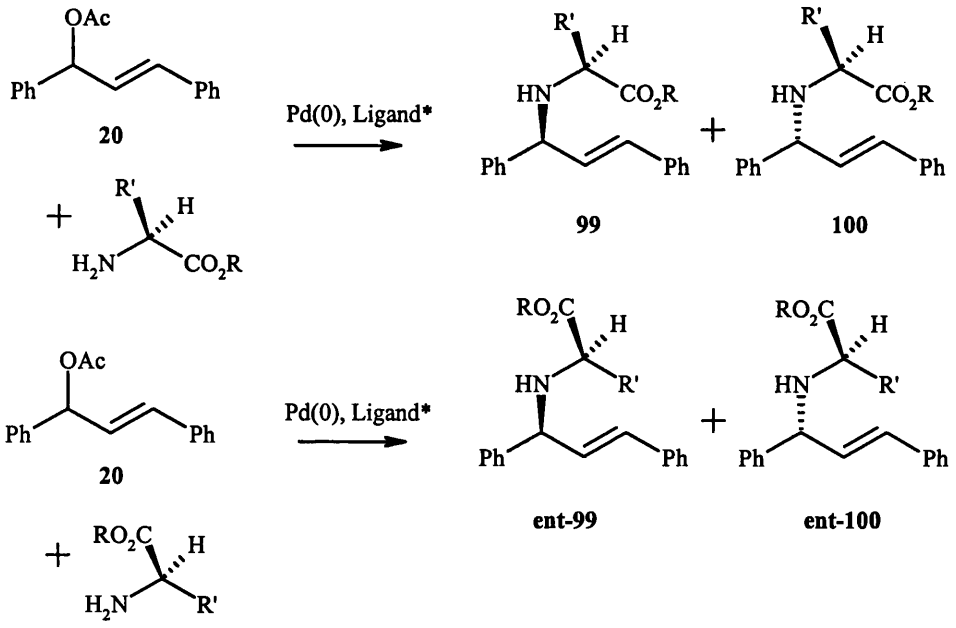


30b



30c

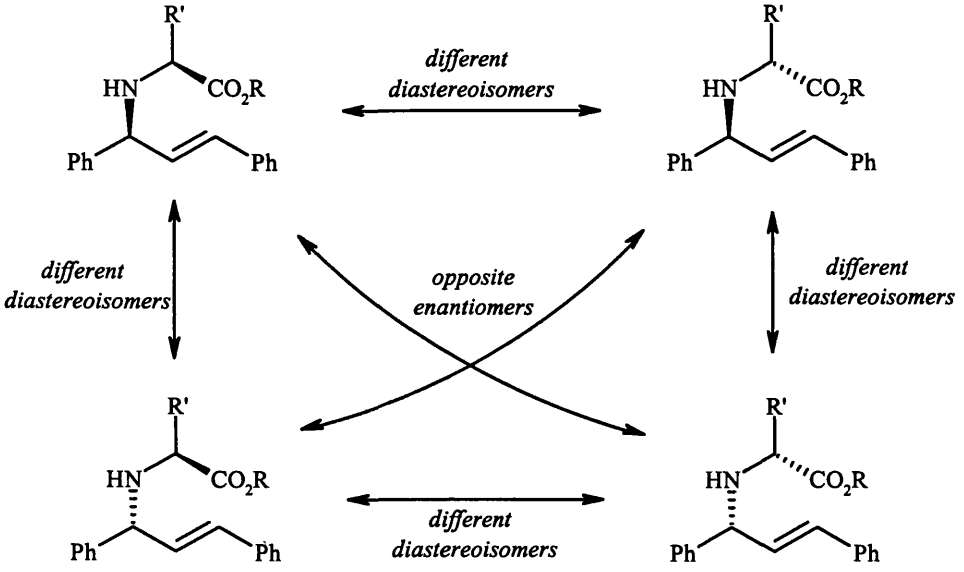
This is advantageous for the analysis of the d.e., with ^{1}H NMR being able to be used. The matched and mismatched combinations can therefore be elucidated by the enantiomer variation of the amino esters with the enantiomerically pure ligands **30a-c**.



The results of the matched and mismatched pairings are shown in Table 3.5. Far higher diastereomeric ratios are obtained when the (*S*)-oxazoline ligand **30a** is in combination with the *D*-amino esters, **ent-98** (entries 2,4,6 and 8) revealing a matched pairing. It is important to note that the directing influence of the ligand is the stronger. For the mismatched pairing, (*S*)-ligand **30a** and amino esters **98**,

the diastereomeric ratios are in favour of the ligands' preference of stereochemistry and not the amino ester nucleophiles' preference. The stereochemistry indicated for the products here is based on the known stereochemical preference of ligand **30a** in palladium catalysed allylic substitution reaction.[105]

Scheme 3.5



The high d.e. values experienced with the isopropyl group of ligand **30a** are not mirrored with the phenyl group of ligand **30b**. The d.e. values obtained from the reactions of both leucine methyl ester enantiomers with the phosphinooxazoline **30b** was small, and the matched/mismatched combinations were hard to resolve with this ligand. It has been shown with prochiral nucleophiles that, in palladium catalysed allylic substitution reactions, the substituent at the stereogenic centre of the ligand has an affect on the e.e. of the product, even though the stereoselectivity is thought to arise as a result of the interactions of the adjacent hydrogen, on the oxazoline of the ligand, in the intermediate palladium complex.

It may be the interaction of the oxazoline R group with the phosphorus phenyl rings that causes these permutations of the e.e. with different ligands in the substitution reaction.

Table 3.5 Diastereomeric ratios of amines **99:100** in asymmetric palladium catalysed substitution with ligands **30a** and **30b**

Entry	Amino ester	Ligand	Yield (%)	Diastereomeric ratio (99:100)
1	**98a**	**30a**	61	84:16
2	**ent-98a**	**30a**	64	91:9
3	**98b**	**30a**	74	78:22
4	**ent-98b**	**30a**	75	91:9
5	**98c**	**30a**	56	58:42
6	**ent-98c**	**30a**	68	74:26
7	**98a**	**30b**	77	68:32
8	**ent-98a**	**30b**	77	65:35

The results from the experiments point to the fact that, the bulkier the R group on the oxazoline the better the d.e. of the amino ester product. Increasing the d.e. of the amino ester products should be achieved by increasing the size of the oxazoline R group from an isopropyl to a *tert*butyl group. Table 3.6 displays the d.e. values obtained from the substitution reactions with oxazoline ligand **30c** making up the palladium catalyst. The high d.e. values recorded with this ligand illustrate that the matched combinations are favoured more strongly with a bulky group on the oxazoline. The best diastereoselectivity is observed with the alkyl side chain amino esters, leucine with a diastereomeric ratio 95:5 and *nor*leucine with an equally impressive ratio of 94:6. The high selectivity when using the

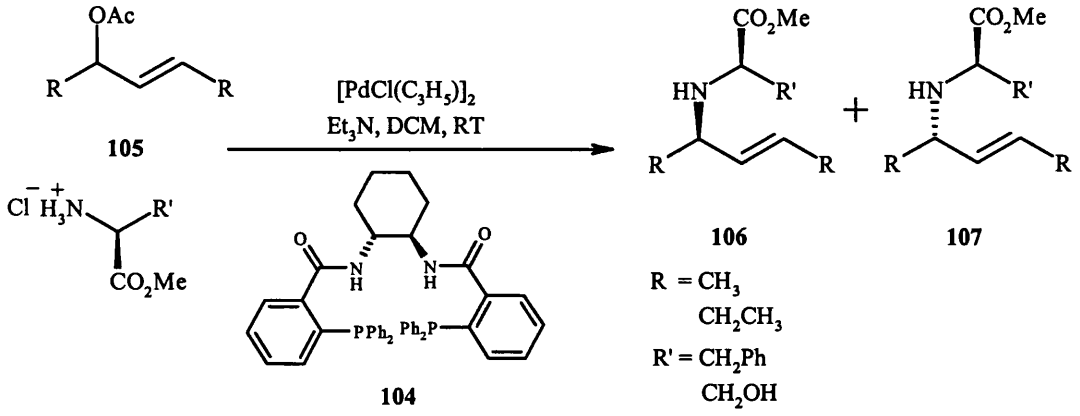
enantiomerically pure oxazoline ligands **30a-c** also help to illustrate how the side chain of the amino ester influences the diastereoselectivity. With the prochiral ligands it was hard to see a trend in the selectivity with changes in the amino ester side chain. Using the asymmetric ligands, the more selective transformations allow smaller changes to be noticed in the products. Better diastereomeric ratios are seen when the side chain position α- to the chiral centre is limited to just a methylene unit; higher substitution at this position (seen with phenyl glycine and valine) reduces the selectivity incurred by the nucleophile. Higher substitution at positions away from the α-position seems not to diminish the affect of the nucleophile, as shown by the excellent d.e. with phenylalanine and leucine nucleophiles.

Table 3.6 Diastereomeric ratios of compounds **99:100** with ligand **30c**

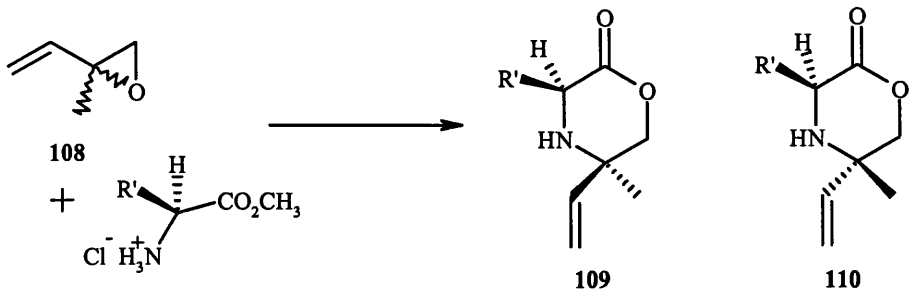
Entry	Amino methyl Ester	Solvent	Yield (%)	Diastereomeric Ratio (99:100)
1	**ent-98a**	THF	75	95:5
2	**ent-98b**	THF	21	61:39
3	**ent-98c**	THF	70	78:22
4	**ent-98d**	THF	87	95:5
5*	**ent-98k**	THF	83	94:6
6	**ent-98a**	Et_2O	89	91:9
7	**ent-98a**	Toluene	46	82:18
8	**ent-98a**	MeCN	27	61:39
9	**ent-98a**	DCM	-	-

*Amino ester **ent-98k** is *D*-Norleucine methyl ester

Trost's palladium catalysed alkylations with amino esters and asymmetric ligands focused predominantly on the stereocontrol generated by the diphosphine ligand **104** to determine the diastereoselectivity of the products. Using only methyl esters of phenylalanine and serine, Trost matched the *L*-phenylalanine methyl ester to the (*R,R*) ligand **104** to give **106** and **107** in an excellent diastereomeric ratio of 95:5 with the pent-2-enyl acetate substrate **105**. The (*S,S*) ligand **ent-104** with *L*-phenylalanine methyl ester gave a lower ratio of 25:75, illustrating the mismatched combination of ligand and nucleophile.[104]



Trost also found that with the hept-2-enyl acetate substrate, even higher diastereomeric ratios are seen with the combination of *L*-serine methyl ester and the palladium catalyst containing the (*R,R*) ligand **104** (diastereomeric ratio 98:2). Trost has applied these highly selective transformations to prepare morpholine derivatives by the palladium catalysed alkylation of allylic epoxide **108** with amino esters glycine, alanine, serine and tryptophan giving diastereomerically enriched products **109** and **110.**



3.4 Conclusion

Enantiomerically pure amino esters have been applied to the palladium catalysed allylic substitution reaction with prochiral catalysts, affording substitution products with diastereomeric ratios of up to 85:15. It has been demonstrated that, if the enantiomerically pure amino esters are combined with enantiomerically pure phosphinooxazoline ligands **30a-c** in the substitution reaction, matched ligand/ nucleophile pairing can be formed resulting in enhanced selectivity in the diastereomeric products, with diastereomeric ratios as high as 95:5 being achieved.

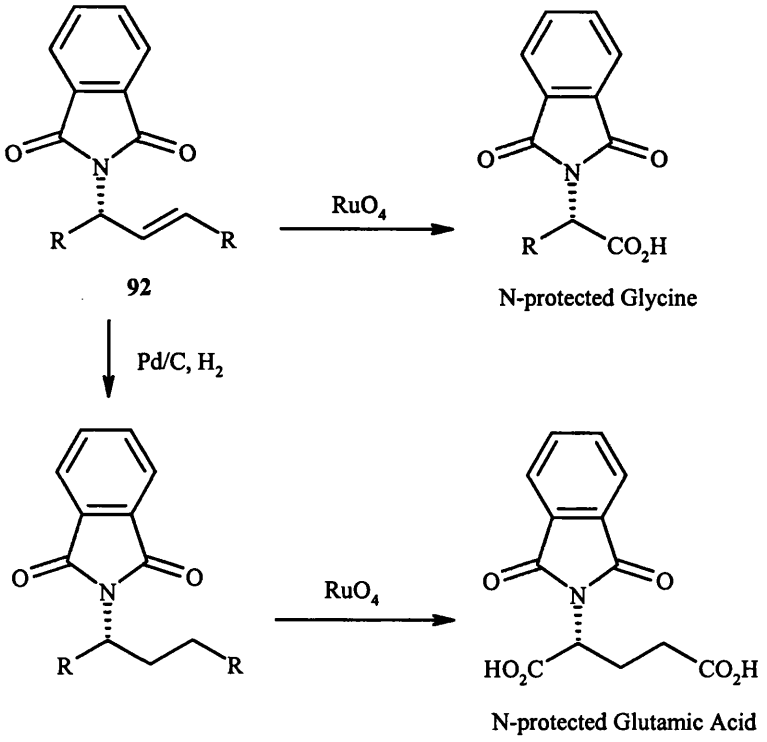
Chapter 4

4 Enantioselective Synthesis of Functionalised Amino Acids

4.1 Introduction

Enantiomerically enriched allylic amines, such as **92**, can be utilised in the preparation of α-amino acids by selective oxidations, affording N-protected amino acids such as glutamic acid and glycine (Scheme 4.1).[84]

Scheme 4.1

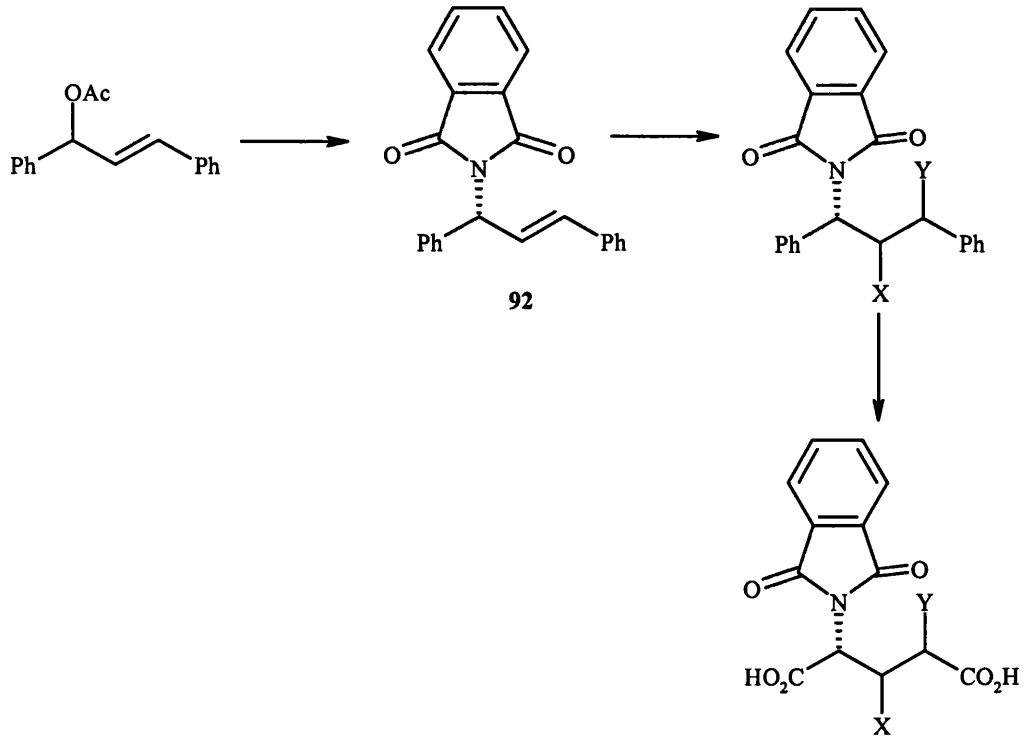


Glutamic acid has been the focus of much research over the years due to its role in many neurodegenerative diseases. We have been interested in preparing enantiomerically enriched functionalised glutamic acid analogues, employing palladium catalysed allylic substitution methodology as a key step to incorporate

asymmetry (Scheme 4.2). It has already been demonstrated that amino acids with functionality at the 2' and 3' positions show strong activity of agonist/antagonist properties for a range of metabotrophic glutamate receptors,[106] indicating possible leads for target compounds against neurological disorders.

We wanted to prepare a range of N-protected amino acids displaying functionality across the 2' and 3' position. The synthetic plan outlined in Scheme 4.2 shows that the derivatisation of the alkene in the substitution product **92** followed by oxidative cleavage of the phenyl rings will afford functionalised amino acids.

Scheme 4.2



4.2 Neurotransmission and glutamic acid

Glutamic acid is one of the major amino acids in the human body, being three to four times more abundant in the brain than any other amino acid. One of the most

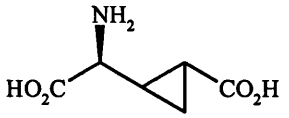
common excitatory neurotransmitters in the mammalian CNS, glutamate is believed to be involved in mechanisms of synaptic plasticity and neuronal cell death.

Despite the significant interest, little is known about the receptors and their precise location and structural features. It is for this reason that selective agonists and antagonists are implemented, in order to learn about the molecular mechanisms of the receptors and to aid the development of novel lead compounds. Many of the agonists and antagonists already known are structural derivatives of *L*-glutamate, having a common (*S*)-configuration with an α-amino acid group one end and an acidic functionality at the other.

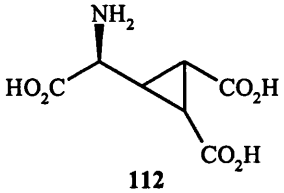
There are known agonists and antagonists of metabotrophic glutamate receptors of which many show structural similarities to *L*-glutamate. Shimamoto *et al* have demonstrated that structures with open (*S*)-configuration in the α-amino acid chain activate mGluR's whereas the folded form stimulates ionotrophic NMDA receptors.[107]

4.3 Cyclopropane glutamic acid analogues

Some of the most promising structures have been the cyclopropylglycines **111** and **112** exhibiting extremely good responses in EC_{50} tests with human Glu2 receptors.[106] These results have led to much research in the area and many groups have synthesised cyclopropylglycine derivatives of this description.[108]

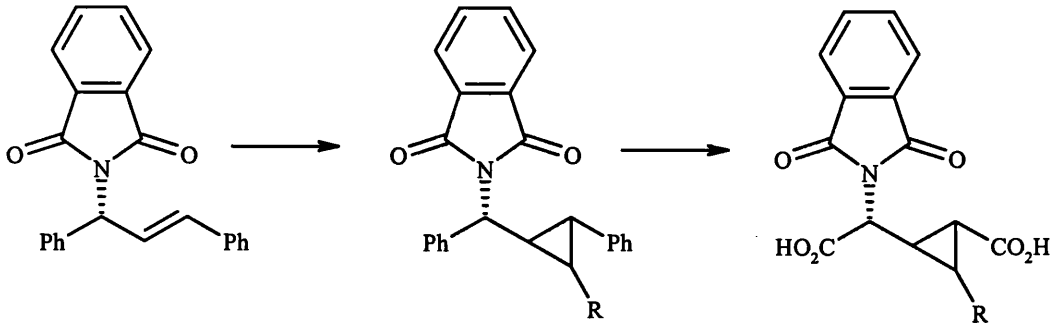


111



112

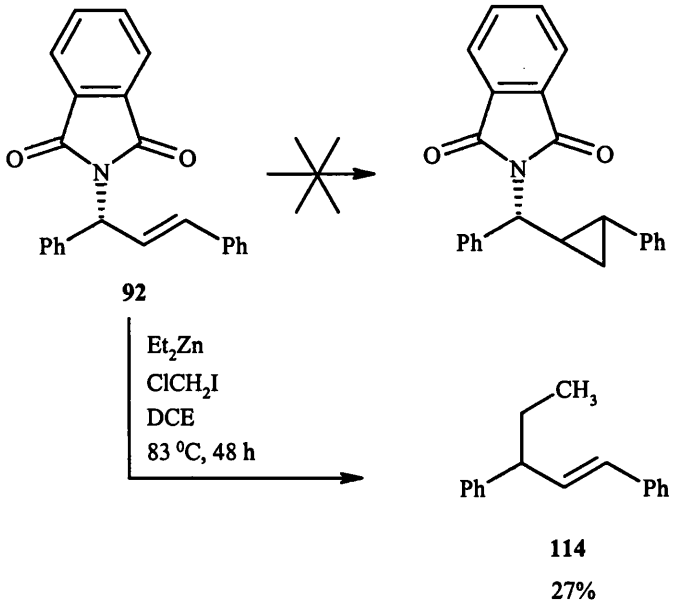
The aim in our research was to prepare cyclopropyl compounds of the form of **113** by first addition of a methylene across the double bond of the allylic amine **92,** followed by oxidative cleavage of the phenyl rings to afford the N protected amino acids **113.**



92 113

Cyclopropane rings are commonly formed from olefins with carbenes by a 1+2 cycloaddition reaction. There are a number of ways to generate carbenes, but most cyclopropane rings are formed using a carbene precursor, eliminating side reactions by not actually isolating free carbenes in the reaction.

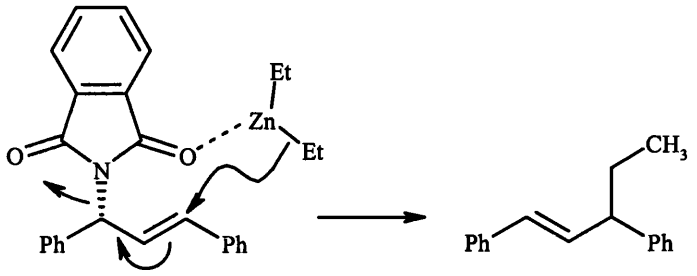
Cyclopropanation on allylic amine **92** was attempted by the modified Simmons-Smith procedure[109] using diethyl zinc and chloroiodomethane. The reaction was performed in anhydrous DCE at room temperature for the first 24 hours followed by heating to reflux for a further 24 hours. The lethargy of the reaction was initially surprising when compared to reaction times cited in the literature.[109] However, after heating to reflux for 24 hours a fraction, more mobile than the starting material, was detected by tlc analysis of the crude reaction mixture.



Work up followed by flash column chromatography separated the new compound from unused starting material. The product displayed an infrared spectrum with no C=O stretch for the phthalimide imide, and the ^1H NMR lacked aromatic phthalimide protons. Further analysis of the ^1H and ^{13}C NMR spectra revealed the presence of methylene and methyl groups in the structure and no signals for the quaternary carbons of phthalimide. This strongly suggested that an ethyl group had displaced the phthalimide functionality. Confirmation of structure **114** for the product was given in the mass spectrum by a MH^+ ion of 223.1.

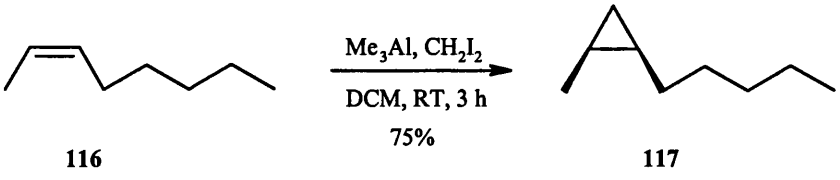
It is proposed that the substitution of the phthalimide was allowed to happen, due to the poor reactivity of the olefin, and co-ordination of zinc to the phthalimide carbonyl which possibly aided the displacement of the imide, resulting in the formation of the alkyl product (Scheme 4.3).

Scheme 4.3

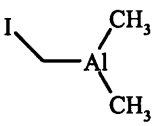


Treatment of olefins with trialkylaluminium species has also been successful in forming cyclopropane rings. The procedure was first demonstrated in 1964 when Miller and co-workers prepared cyclopropane rings from alkenes using triethylaluminium-methylene iodide in cyclohexane.[110] Poor yields were experienced by Miller, which he explained was due to the instability of the dialkyl(α-iodoalkyl) aluminium species **115**.

More recently Yamamoto and co-workers revisited the reaction and found that the choice of solvent had a profound influence on the stability of intermediate **115**. Using dichloromethane as the solvent, excellent yields have been seen by Yamamoto in transformations such as the *cis* olefin **116** to the cyclopropane derivative **117**.[111]

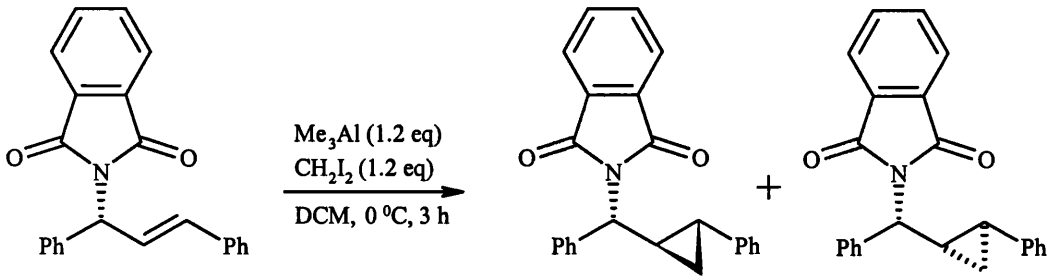


116 **117**



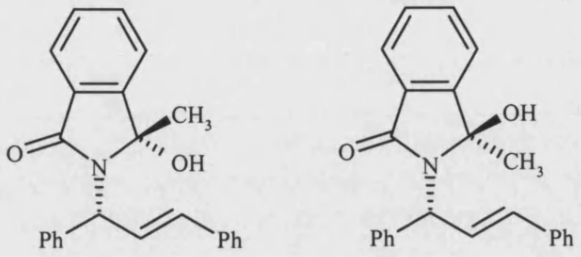
115

Applying Yamamoto's reactions conditions, we reacted olefin **92** with trimethylaluminium and diiodomethane in dry dichloromethane at 0 °C for 3 hours. The formation of two new compounds together with the starting substrate, observed by tlc analysis, gave initial thoughts of cyclopropane derivatives **118** and **119**.



92 **118** **119**

The mass spectra of both products gave identical M^+ ions of 355.1. This molecular weight suggested the introduction of a methyl group and not a methylene unit to the substrate. Spectroscopic analysis supported this notion. Both compounds had very similar ^1H NMR spectra, each displaying a methyl singlet at δ1.6 and olefin signals at δ6.5 and δ7.0. There were also no signs of the characteristic proton signals at very high field for the cyclopropane hydrogens. A broad singlet between δ2-3 suggested the presence of a hydroxy group in the product, and this was confirmed by the disappearance of the peak on a D_2O shake and a strong wide peak at 3290cm^{-1} in the infrared spectrum. Combining this information to the appearance of six quaternary centres in the ^{13}C NMR spectrum and disruption to the phthalimide coupling patterns in the ^1H NMR suggested compounds **120** and **121** for the products.



120 **121**

The X-ray structure in Figure 4.1 confirms the structure of alcohol **120**. To demonstrate that the second product **121** is the isomer of alcohol **120**, enantiomer **120** was dissolved in acetone and stirred for 2 hours with catalytic amounts of conc. HCl. Epimerisation of the alcohol centre resulted in the appearance of both compounds **120** and **121** in the reaction vessel Scheme 4.4).

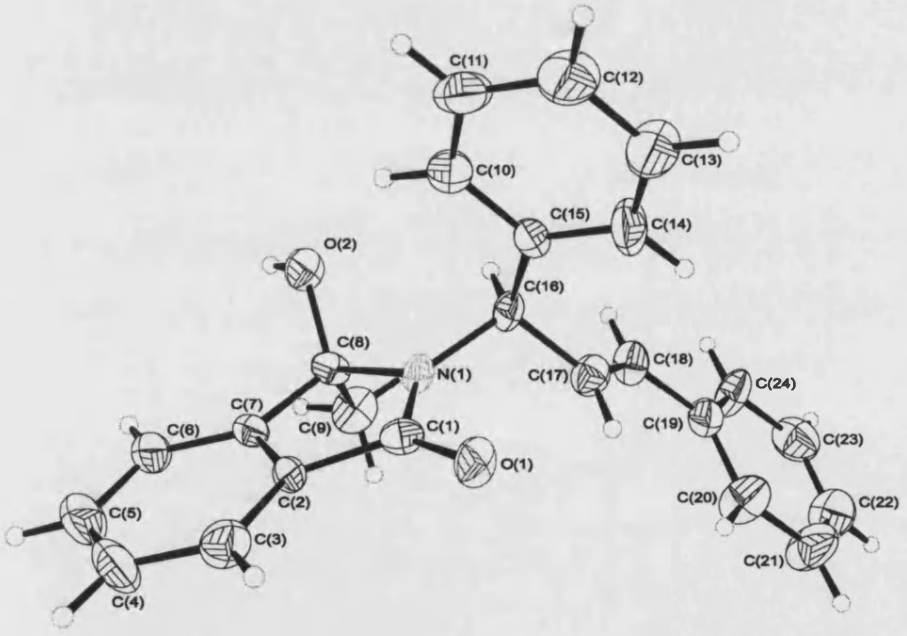
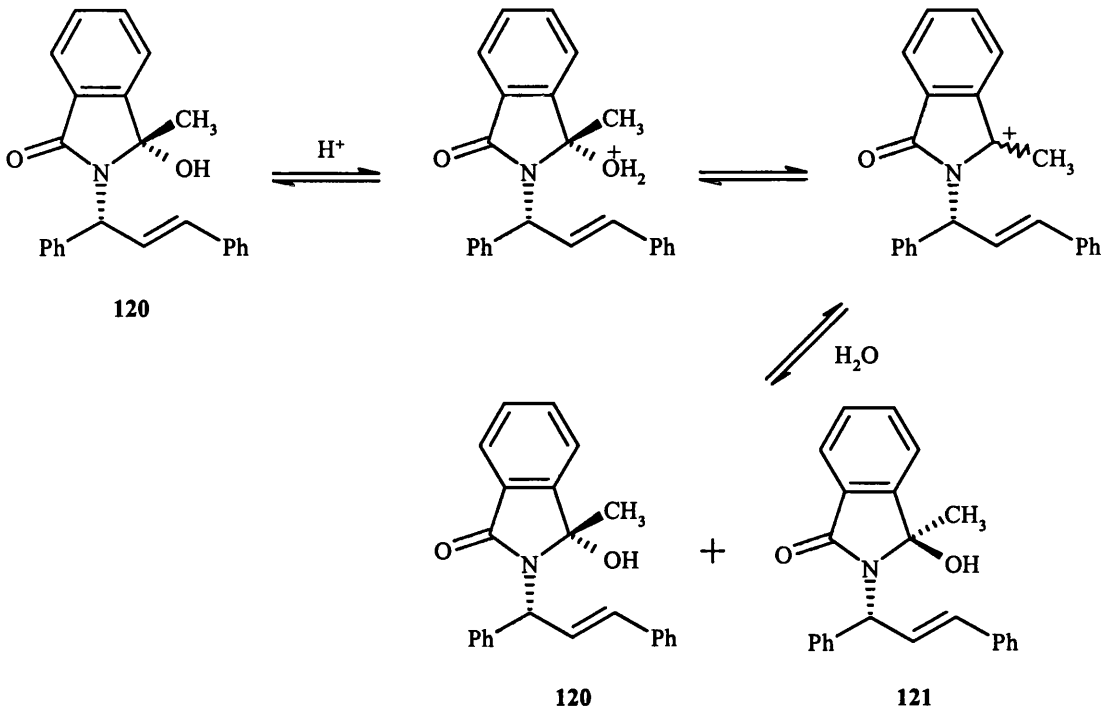


Figure 4.1 Crystal structure of **120** showing the labelling scheme used. Thermal ellipsoids are represented at the 30% probability level (for supplementary data to Figure 4.1 (compound **120**) see Appendix B).

Scheme 4.4



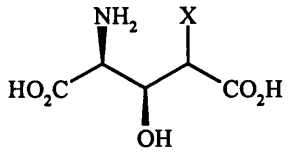
120 **120** **121**

Alternative procedures also attempted for the cyclopropanation of allylic amine **92** were; dirhodium catalysed addition of diazoethyl acetate,[112] palladium catalysed addition of diazoethyl acetate,[113] diazomethane addition with palladium acetate[114] and samarium promoted cyclopropanation with diiodomethane.[115] None of these procedures gave the desired cyclopropane ring from the starting allylic amine **92**.

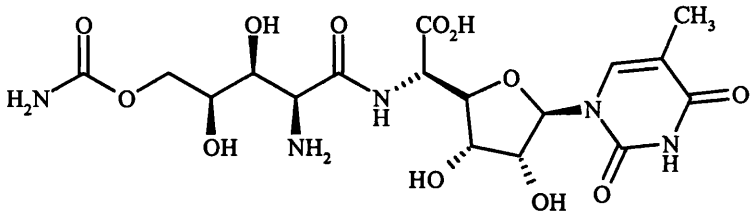
4.4 Hydroxy glutamic acid analogues

Hydroxy glutamic acids of the form **122** have also stimulated wide interest due to the interesting biological applications for potential excitatory amino acids

antagonists,[116] as well as their usefulness as chiral synthetic intermediates for the preparation of natural products such as the polyoxin J **123**.[117]

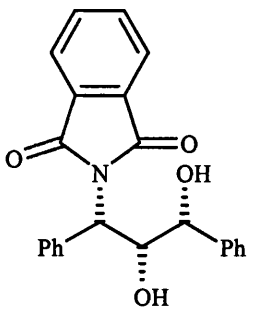


122 X = H, OH, CH_3

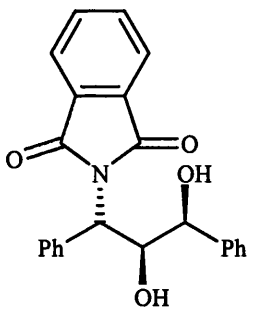


123

The preparation of hydroxy derivatives were investigated by the oxidation of the olefin in amine **92**. Previously, in this research group, asymmetric dihydroxylation of the amine **92,** utilising Sharpless methodology and AD-mixes, gave the *cis* diols **124** (*R,R*-diol) in 87% d.e. (56% yield) and **125** (*S,S*-diol) in 95% d.e. (62% yield).[118]



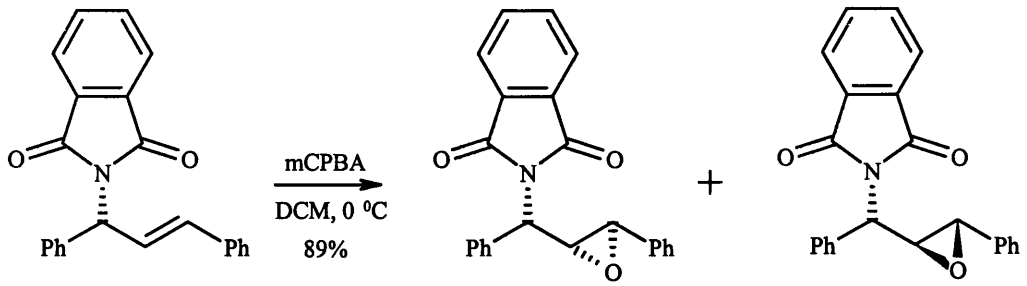
124



125

In the interest of preparing the *trans* diol, epoxidation of the olefin would create the additional asymmetric centres with the correct stereochemistry. Epoxidation

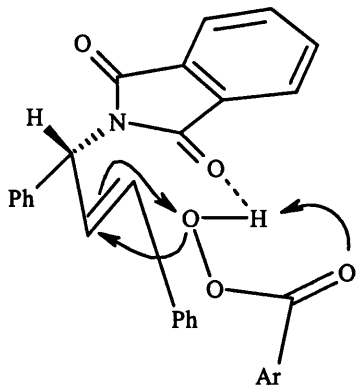
was accomplished by the treatment of alkene **92** with *meta*-chloroperbenzoic acid in DCM at 0 °C over 24 hours. The presence of two sets of signals in the ^{1}H NMR for the oxirane protons allowed the diastereomeric ratio of epoxides **126** and **127** to be measured.



92 **126** **127**

A ratio of 9:1 was observed in the spectrum showing strong stereocontrol by the peracid in the reaction. This selectivity can be explained by the co-operative co-ordination of the peracid by hydrogen bonding to the imide carbonyl of the phthalimide, facilitating concerted attack on the olefin predominately on the same face as the phthalimide (Scheme 4.5).

Scheme 4.5



Stereoselective epoxidations using mCPBA have also been reported by other research groups. Kocovský and co workers[119] have shown that carbamates in non-coordinating solvents are oxidised in a *syn* fashion to afford *cis* epoxides, while Kogen[120] supports the idea of hydrogen bonding of the peracid to the carbonyl of the amide, to aid *syn* attack. Other examples of the formation of *cis* epoxides by co-operative co-ordination of the peracid have been shown by, Luthman *et al* using carbamates and esters,[121] and by Albeck *et al* where hydrogen bonding of the peracid to the NH of the amide gave the selectivity.[122]

Crystallisation of the major isomer **126** from dichloromethane and diethyl ether afforded the diastereomerically pure (1*S*,2*R*,3*S*) epoxide **126** as confirmed by the X-ray crystal structure in Figure 4.2.

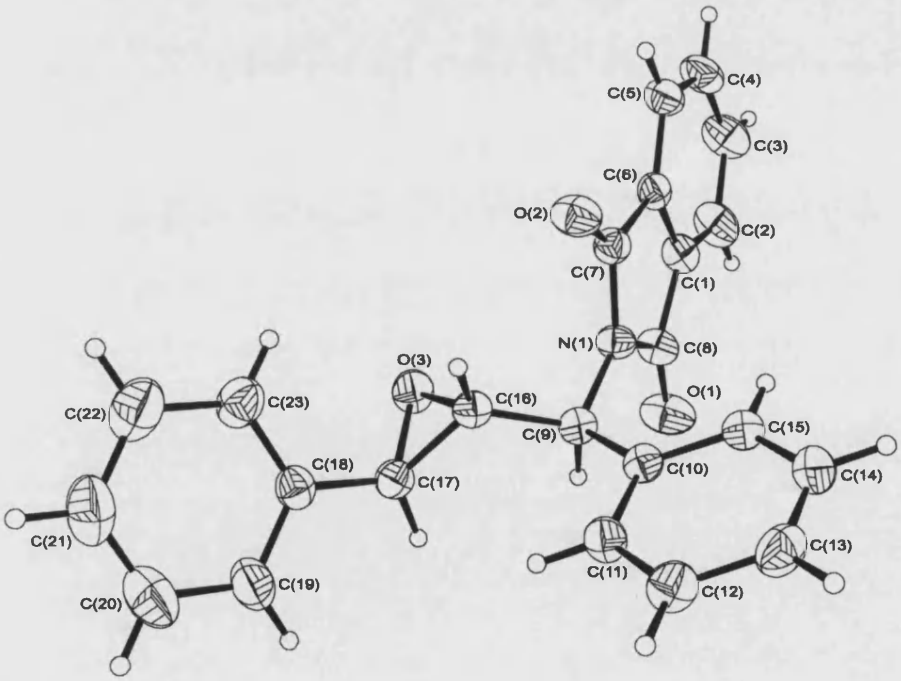
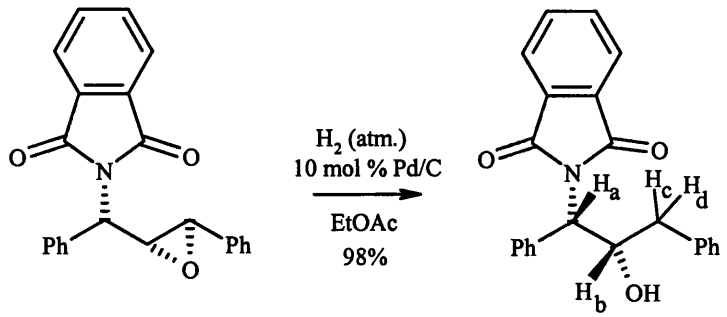


Figure 4.2 Crystal structure of **126** showing the labelling scheme used. Thermal ellipsoids are represented at the 30% probability level (for supplementary data to Figure 4.2 (compound **126**) see Appendix C).

Isolation of the diastereomerically pure epoxide allows a variety of hydroxy analogues, possessing three adjacent chiral centres, to be formed by the stereo- and regio- controlled ring opening of the oxirane ring.

Reduction of epoxide **126** is anticipated to be regioselective in producing the (1*S*)-phthaloyl-(2*S*)-2-hydroxy-1,3-diphenylpropane **128** because of the electronic activation of the centre adjacent to the phenyl ring. There are numerous reagents available for the reduction of an epoxide to an alcohol.[123] Hydrogenation of epoxides with atmospheric hydrogen and a palladium/carbon catalyst has been shown to be a very attractive route to access the mono alcohol cleanly in high yields.[124] Thus, epoxide **126** in ethyl acetate was stirred vigorously for 48 hours with a catalytic amount of 10% palladium on carbon under a balloon of hydrogen. A single product was isolated from the reaction displaying a molecular weight of 358.1. The presence of a broad peak at 3460cm^{-1} in the infrared spectrum and a singlet at δ1.63 in the ^{1}H NMR showed the existence of the hydroxy functionality.



126 **128**

The proton splitting patterns of the alkyl chain in the ^{1}H NMR spectrum (H_b being a doublet of triplets and H_c and H_d being doublet of doublets) supported the regiochemistry illustrated in structure **128**. The X-ray crystal structure in Figure 4.3 confirms the stereochemistry and the regiochemistry of the alcohol.

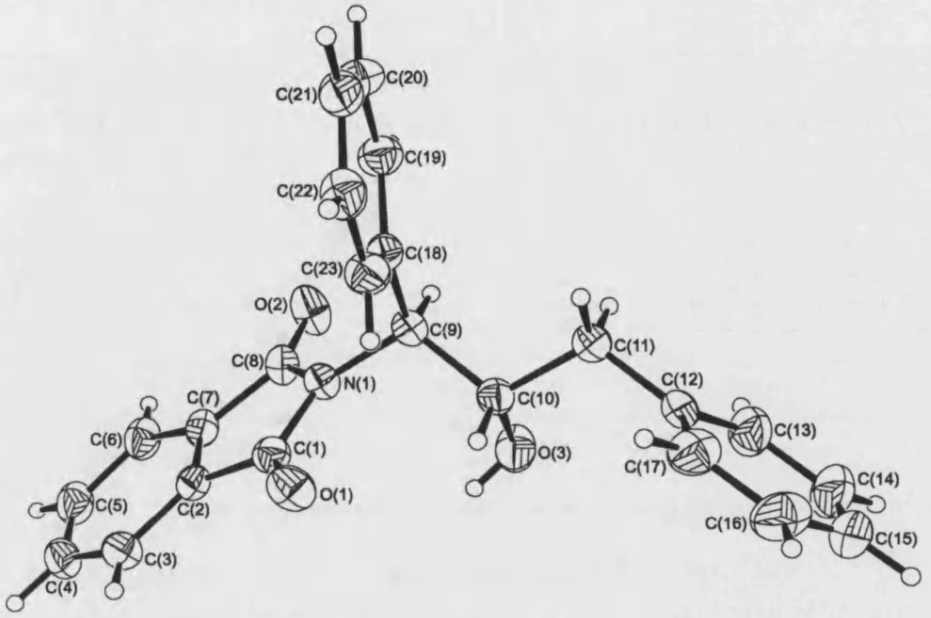
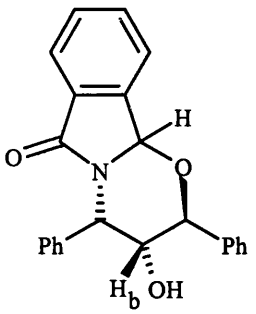


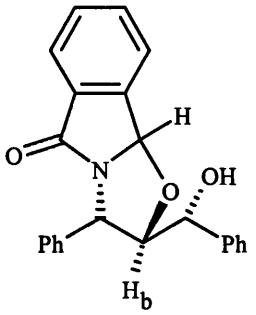
Figure 4.3 Crystal structure of **128** showing the labelling scheme used. Thermal ellipsoids are represented at the 30% probability level (for supplementary data for Figure 4.3 (compound **128**) see Appendic D).

Initial attempts to reduce epoxide **126** with metal hydride sources, such as sodium borohydride[125] and sodium cyanoborohydride/boron trifluoride etherate[126] were unsuccessful. Both reducing agents gave the same two products from the reactions. The compounds had a molecular ion of 358.1, consistent with structure **128**. ^{1}H NMR analysis also showed the presence of OH signals in the two compounds, however, the other peaks in the spectra were quite different to the data from alcohol **128**. In both spectra there were proton singlet peaks at very low field (δ6.3) and the three alkyl chain methine signals were all at lower field (δ4-6) than in the spectrum of alcohol **128**. ^{1}H-^{1}H COSY analysis of the more polar compound revealed coupling between the hydroxy proton and the central CH proton, H_b, of the alkyl hydrocarbon chain. In the ^{13}C NMR six quaternary

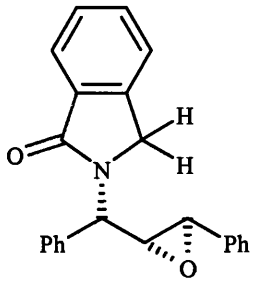
carbons were present (as in compounds **120** and **121**) suggesting disruption to the phthalimide moiety. Further NMR study concluded that the more polar of the two compounds corresponded to structure **129**.



129



130

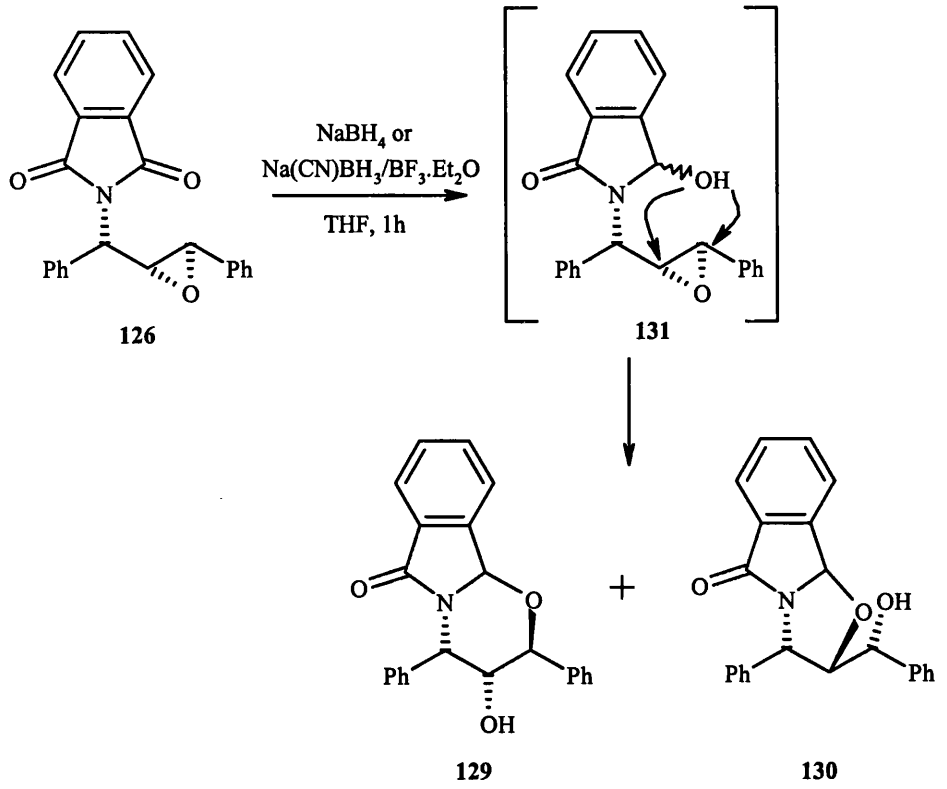


131

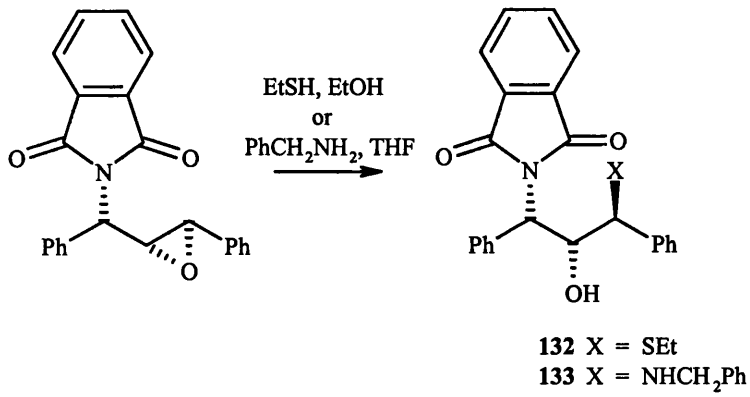
For the second product, cyclic ether **130** and epoxide **131** were suggested. Both structures could be seen to give similar splitting patterns in the spectroscopic data. Alcohol **130** was chosen for the product on the basis of the coupling constants. First, there was no sign of coupling between the OH peak and the methine protons in the carbon chain, and second, the coupling constants for the methine C*H*O protons were not consistent for the presence of an epoxide.

The formation of the two cyclic ethers is proposed first by the reduction of the phthalimide to the intermediate **131** which then ring opens the epoxide to give the two isomers **129** and **130** (Scheme 4.6).

Scheme 4.6

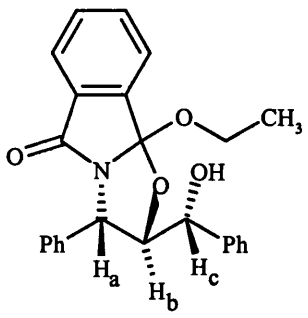


Similar cyclic ethers are also observed in the attempted formation of hydroxy thiol **132** and hydroxy amine **133**.

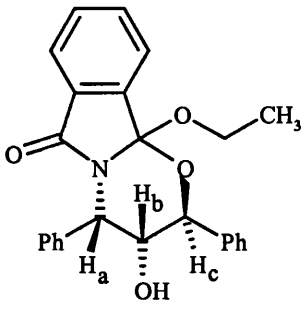


For the thiol reaction, the major product isolated after flash column chromatography was a straw coloured oil with a molecular ion FAB+ of 402.1. A molecular ion of MH^+ 418 is required for desired thiol **132**, however, the observed ion would agree with the introduction of an ethoxy group into the molecule. ^1H

NMR analysis indeed showed the characteristic patterns for an ethoxy functionality, displaying a triplet at δ1.23 of intensity 3 and two quartets at δ3.98 and δ4.11. The ^{1}H NMR spectrum also showed disruption to the splitting of the phthalimide protons while the ^{13}C NMR showed the presence of non-equivalent quaternary carbons for the phthalimide moiety. As with structure **130** the size of the cyclic ether was tentatively assigned by the coupling of the hydroxy proton to the alkyl CH protons. The observed doublet of doublets for proton H_c coupled to the OH is in agreement with the 5-membered cyclic ether **134**. If the 6-membered ring structure **135** is considered, a double doublet of doublets would be seen for H_b, and this is not observed.



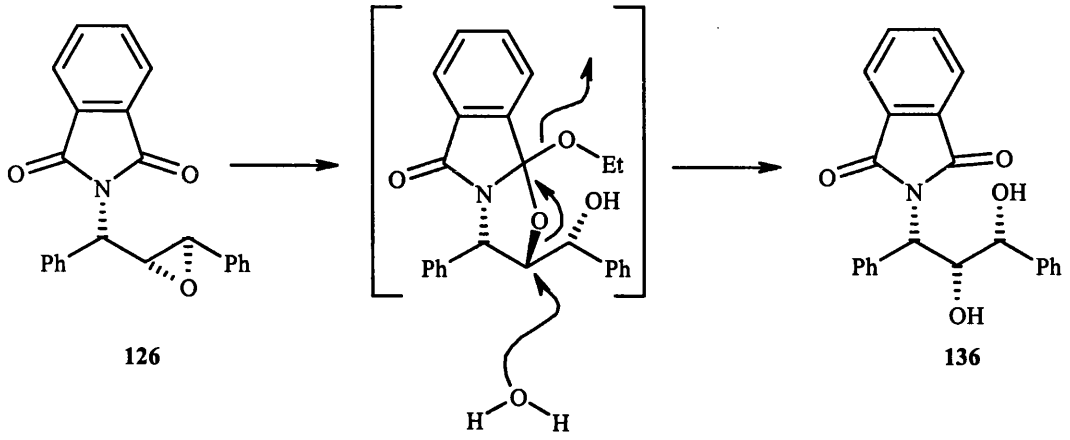
134



135

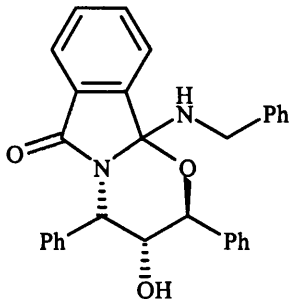
Trying to reproduce the formation of acetal **134** from epoxide **126** by heating the compound **126** to reflux in dry ethanol (without ethanethiol) resulted in the formation of the *cis* diol **136** as the major product. Acetal **134** was initially seen in the reaction mixture by tlc analysis and by crude ^{1}H NMR. However, as the reaction proceeded the conversion of the acetal intermediate to the diol progressed, eventually affording a high yield (91%) of the diol **136**. The ^{1}H NMR spectrum of diol **136** was seen to be identical to that of the *cis* diol **124** confirming the compound as the (1*S*,2*R*,3*R*)-*N*-phthaloyl-2,3-dihydroxy-1,3-diphenylpropane

molecule. It is suggested that the formation of the diol is due to trace amounts of water in the reaction causing the collapse of the acetal to compound **136**.



126 **136**

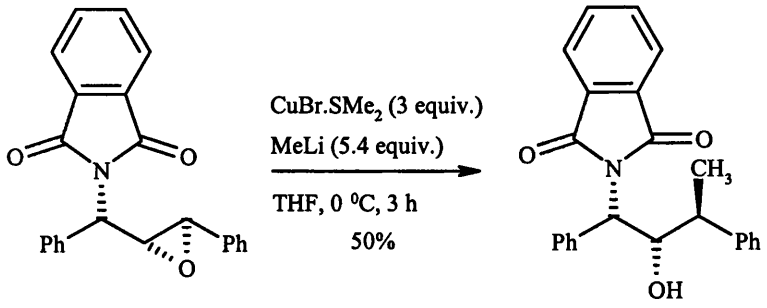
Similar nucleophilic attack on the phthalimide was also observed with amine nucleophiles and carbon nucleophiles. The addition of benzylamine to epoxide **126** in THF at room temperature resulted in the formation of lactam **137** after 48 hours of stirring.



137

Initial use of organolithium[127] reagents and Grignard reagents[128] also saw attack at the carbonyl. For the selective attack at the epoxide in compound **126**, softer cuprate nucleophiles were seen as an alternative. The heterocuprate reagent, MeCu(CN)Li,[129] and the higher order cuprate, $MeCu(C_4H_3S)CNLi_2$,[130] both proved unreactive to epoxide **126**. Success was obtained with copper bromide dimethylsulfide complex combined with methyl lithium.[131] The product **138**

displayed a high resolution mass spectrum M^+ of 372.1603 consistent with the desired product. In the ^1H NMR, a doublet at δ1.39 for the methyl group demonstrated the insertion of the nucleophile into the alkyl chain, and the symmetrical nature of the phthalimide protons peaks together with only four quaternary carbons being observed in the ^{13}C NMR spectrum also illustrated an intact phthalimide moiety.



126 **138**

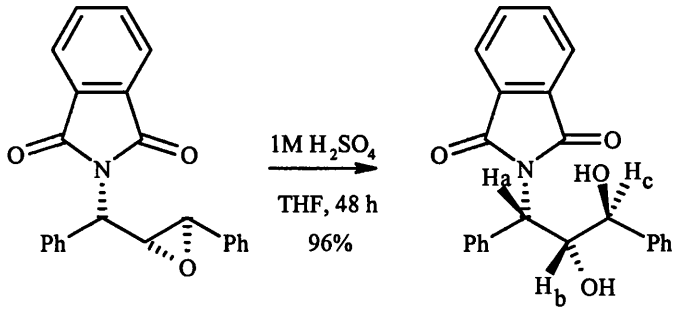
Reactions were performed initially with 3 equivalents of copper bromide dimethyl sulfide and 6 equivalents of methyl lithium per equivalent of substrate, resulting in a mixture of products, with alcohol **138** only being isolated in 14% yield. Cleaner reactions were observed when less than 2 equivalents of methyl lithium was used per equivalent of copper bromide dimethyl sulfide, insuring that no excess organo lithium reagent remained in the vessel to react with the epoxide. Changing to methyl magnesium bromide from methyl lithium, combined with running the reaction at a higher temperature, also gave an improvement in yield. Using less than 3 equivalents of the cuprate resulted in incomplete reactions. For example, using 1.25 equivalents of cuprate gave only a 18% yield of alcohol **138**, with 60% starting material, while 2 equivalents of cuprate increased the yield to 41% of compound **138**. The best conditions found were to use 3 equivalents of

copper bromide dimethyl sulfide with 5.4 equivalent of methyl magnesium bromide while running the reaction between –10 and 0°C (Table 4.1).

Table 4.1 Yields of alcohol **138** with variation in amount of cuprate and temperature

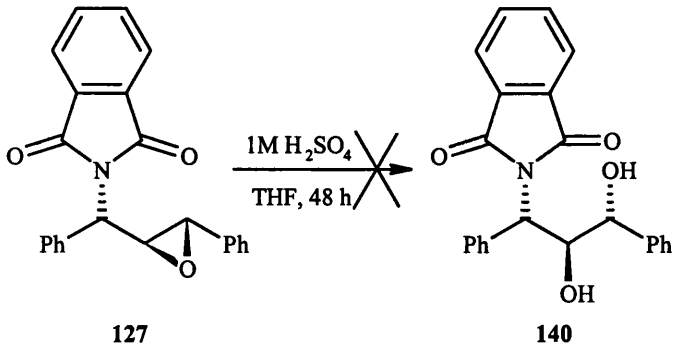
Cuprate (equiv.)	Alkyl Metal (equiv.)	Temp. (°C)	Yield %
$CuBr.SMe_2$ (3)	MeLi (6)	-78	14
$CuBr.SMe_2$ (3)	MeLi (5.4)	-25	15
$CuBr.SMe_2$ (3)	MeLi (5.4)	-10-0	25
$CuBr.SMe_2$ (1.5)	MeLi (2.85)	-15	11
$CuBr.SMe_2$ (1.25)	MeMgBr (2.25)	-15	18
$CuBr.SMe_2$ (2)	MeMgBr (3.8)	-10-0	41
$CuBr.SMe_2$ (3)	MeMgBr (5.4)	-10-0	50

The epoxide may also be opened to give the *trans* diol by acid catalysed hydrolysis. Treatment of the epoxide in THF with dilute sulphuric acid over 48 hours at room temperature gives the *trans* diol **136** exclusively. Coupling in the proton NMR data of the two OH peaks with protons H_b and H_c gives complex signals for the alkyl protons. However, addition of D_2O to the sample collapses the peaks to, a distinct double of doublets for H_b at δ 5.91, and a doublet for H_c at δ4.53.

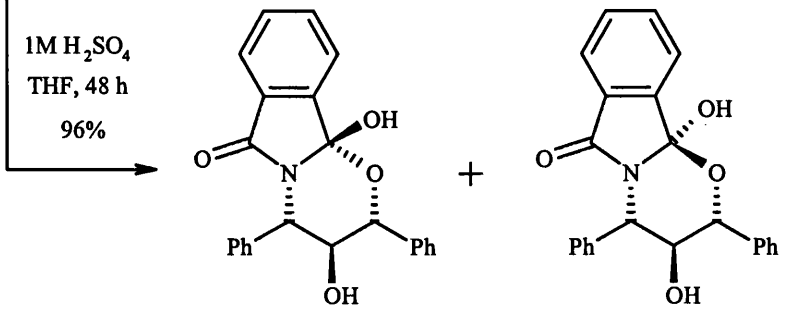


126 **139**

Interestingly the acid catalysed hydrolysis of the minor epoxide **127** did not yield the corresponding *trans* diol **140**. A molecular ion of MH^+ 374.1 and a strong broad stretch in the infrared suggested that the diol had been formed. However, in the ^1H NMR data two sets of signals were observed for the three alkyl protons, H_a, H_b and H_c. The inference for isomers was strengthened by the ^1H-^1H COSY spectra that revealed coupling existed between protons in the same set but not between the two different sets. As detected previously for compounds **120, 121, 129, 130, 134, 135** and **137** the protons on the phthalimide functionality were disrupted, and ^{13}C NMR also displayed six quaternary carbon centres. We therefore think that on addition of dilute acid to epoxide **127**, the isomers **141** and **142** are formed. The fact that this reaction only takes place with epoxide **127** is probably due to the favourable positions of the hydroxy group and carbonyl of the phthalimide in this stereoisomer.

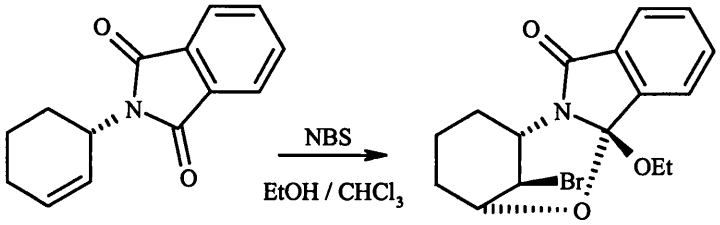


127 **140**



141 **142**

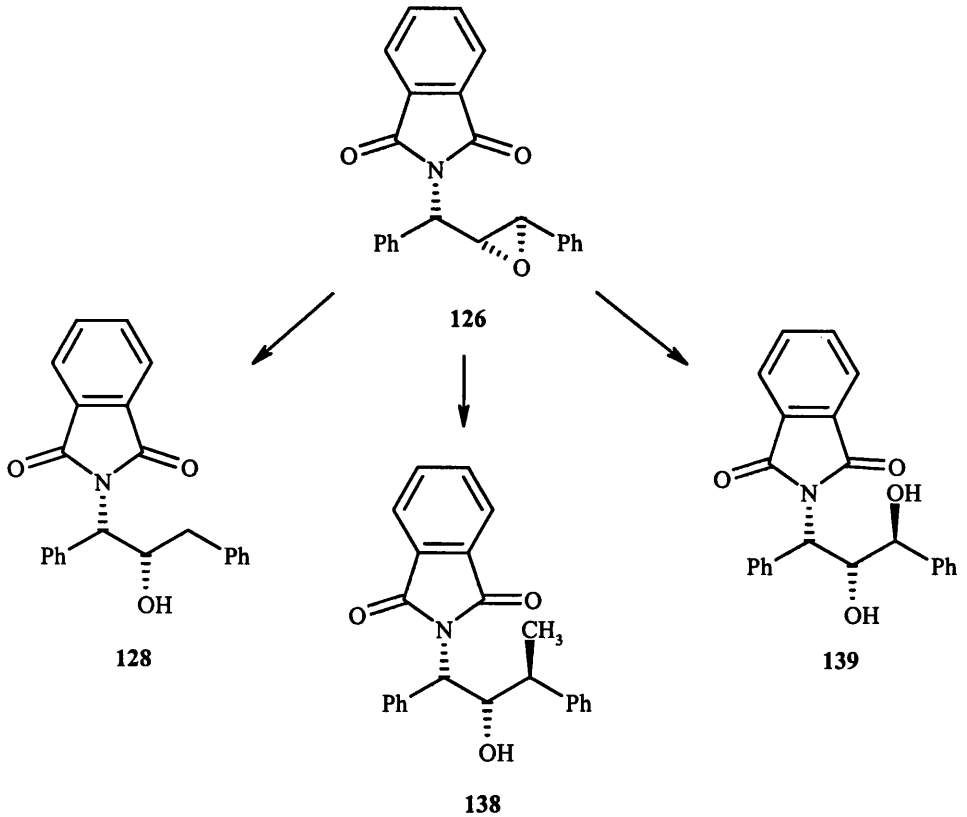
The tendency of the phthalimide moiety to react with nucleophiles resulting in cyclic ether structures has been seen before in the literature. Sammes *et al* have reported that the reaction of amide **143** with N-bromosuccinimide in ethanolic chloroform gave the bromo compound **144** as the sole product.[132] It would appear that the correct geometry greatly enhances the chance of intramolecular nucleophilic attack on the phthalimide to give these cyclisations.



143 **144**

4.5 Conclusion

The enantiomerically enriched palladium catalysed allylic amination product **92** proved unreactive to cyclopropanation using a range of cyclopropanation procedures. The enantiomerically enriched allylic amine **92** was successfully epoxidised using *m*CPBA, giving a stereoselective reaction by co-operative co-ordination of the peracid to the phthalimide, affording a 9:1 ratio in favour of the *cis* epoxide. Stereo- and regio-selective ring opening of the epoxide with carbon, oxygen and hydride nucleophiles, gave N- and C-terminus protected functionalised glutamic acid analogues possessing three adjacent asymmetric centres.



Chapter 5

5 Ruthenium Tetraoxide Oxidations

5.1 Introduction

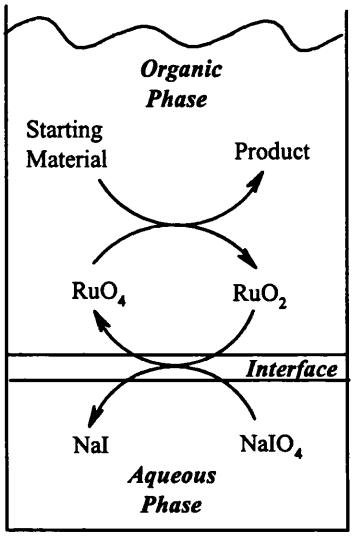
The utility of ruthenium tetraoxide as an organic oxidant has been recognised for some time. In 1953 Djerassi and Engle[133] were the first to oxidise organic compounds with ruthenium tetraoxide and since that date many oxidative transformations have been accomplished with this reagent.

Initially ruthenium tetraoxide was prepared in stoichiometric amounts by oxidation of ruthenium trichloride or ruthenium dioxide with aqueous periodate or hypochlorite and then extracted into carbon tetrachloride. Ruthenium sources are however expensive, and so catalytic procedures evolved. The most popular method adopted was to use catalytic amounts of the ruthenium trichloride or ruthenium dioxide with stoichiometric amounts of a co-oxidant in a biphasic system. It is assumed that the oxidation of the substrate with ruthenium tetraoxide takes place in the organic phase. The consumption of the ruthenium tetraoxide in the oxidation generates ruthenium dioxide, which is neither soluble in organic or aqueous phases and migrates to the interface of the solvents. Oxidation of the ruthenium species by the co-oxidant generates the RuO_4 catalyst again. The best results are therefore experienced when the mixture is stirred or shaken vigorously (Scheme 5.1).

The co-oxidant used can be either sodium hypochlorite,[134] sodium bromate,[135] periodic acid,[136] peracetic acid,[135] sodium periodate,[137] oxygen,[138] cerium sulfate,[139] potassium permanganate[139] or oxone[140] in a biphasic system of carbon

tetrachloride and water. With the most common co-oxidants, periodate and hypochlorite, it was noted by many research groups that often sluggish or incomplete reactions were encountered, especially when oxidising to carboxylic acid products.[137] Sharpless *et al* speculated that in the course of the reaction, lower valent ruthenium carboxylate complexes might be responsible for the loss of catalyst activity.[137]

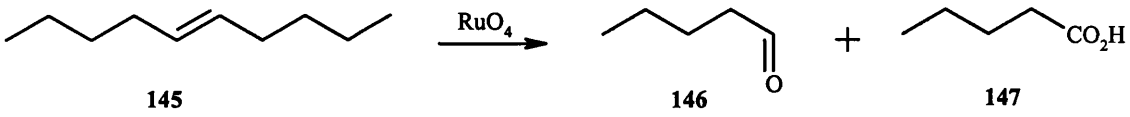
Scheme 5.1



To test this theory, Sharpless and co-workers used a Ru(II)/Ru(III) mixed valent oxo-triruthenium carboxylate complex $[(Ru_3O(OAc)_6(H_2O)_3^{+}\cdot OAc]$ as an oxidation catalyst for the cleavage of 1-octene to pentanoic acid. The catalyst indeed proved inactive. However, on addition of acetonitrile to the inactive system, rapid oxidation of the substrate was observed affording pentanoic acid. Acetonitrile disrupts the insoluble carboxylate complexes formed in the reaction and also helps return the ruthenium to the catalytic cycle. The optimum ratio for the solvents is carbon tetrachloride, acetonitrile and water in a 2:2:3 mix. The impressive results obtained by Sharpless for the oxidation of (*E*)-5-decene with

this new solvent system, compared to two other commonly used solvent systems acetone/water and carbon tetrachloride/water[137] (Scheme 5.2), eventually saw the carbon tetrachloride/acetonitrile/water solvent combination uniformly used for ruthenium tetraoxide oxidations in organic chemistry.

Scheme 5.2



145 146 147

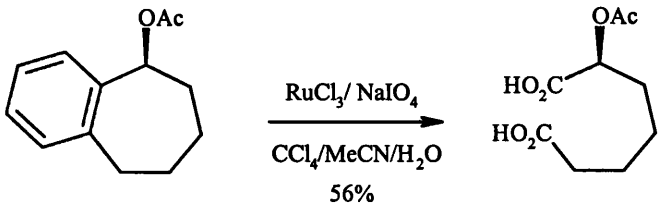
Solvent	Yield (%)	145	146	147
CCl_4/H_2O (1:1)		80	17	0
Acetone/H_2O (5:1)		74	20	3
CCl_4/MeCN/H_2O (2:2:3)		0	0	88

Sharpless *et al* commonly used sodium periodate as the co-oxidant in ruthenium tetraoxide formation, but the insoluble NaI precipitate from the reaction often prevented the oxidations going to completion. Periodic acid, on the other hand, has been shown by Martín and co-workers to be a very efficient alternative without the problems of precipitation.[136] Periodic acid seems particularly advantageous for oxidative cleavage of aromatic rings where a large excess of co-oxidant is needed. However, it must be noted that where acid sensitive groups are present the sodium periodate system is better.

A typical procedure for the oxidation, for example of (*E*)-5-decene, is as follows. To alkene **145** (1mmol) in CCl_4 ($2cm^3$), CH_3CN ($2cm^3$) and H_2O ($3cm^3$) is added $NaIO_4$ (4.1 mmol). After 5 minutes of stirring at room temperature ruthenium trichloride (2 mol%) is added and the mixture is vigorously stirred (with water

cooling) until the reaction is complete and a pale yellow colour of RuO_4 persists in the organic phase. The reaction mixture is then diluted with dichloromethane ($10cm^3$) and H_2O ($20cm^3$) and the organic fraction separated. The aqueous is back-extracted with dichloromethane ($10cm^3$x4) and the combined organic fractions dried ($MgSO_4$). The crude product is then either purified by bulb-to-bulb distillation or by silica gel flash column chromatography.

Ruthenium tetraoxide has become a popular choice in organic synthesis due to its strong oxidising abilities under relatively mild conditions (usually a few hours at room temperature). It also has the ability to oxidise reaction sites close to a stereogenic centre and leave the stereochemistry unaffected, as seen in the formation of the diacid **149** from the acetate **148**.[141]

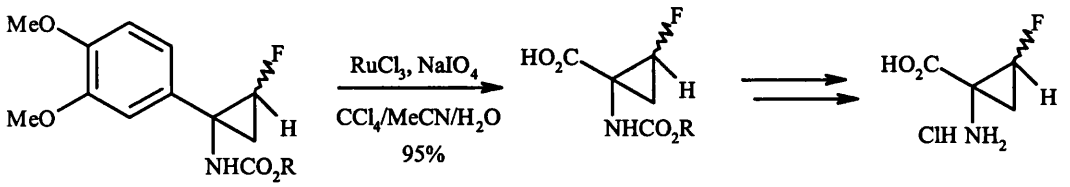


148 **149**

Ruthenium has been applied to many oxidative transformations, non-bond breaking (primary alcohols to carboxylic acid,[142] secondary alcohols to ketones,[143] aldehydes to carboxylic acids,[144] primary alkyl iodides to carboxylic acids,[145] sulfites to sulfates,[146] alkyl ethers to esters,[147] cyclic ethers to lactones,[137] amines to nitriles and amides[148] and cyclic amines to lactams[149]) and bond breaking (alkenes to carboxylic acids,[150] diols to carboxylic acids[137,151] and aromatic rings to carboxylic acids[136,137,141,152]). It is ruthenium tetraoxide's greater vigour that

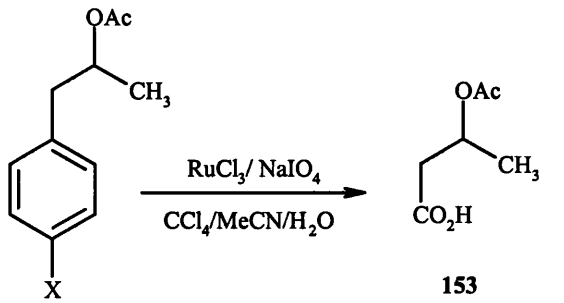
allows the cleavage of carbon-carbon bonds, and which separates it from other metal centred oxidants such as osmium tetraoxide.

The oxidation of aromatic rings with ruthenium tetraoxide has opened up great avenues in organic synthesis. The reactive carboxylic acid moiety can now be masked using the relatively inert phenyl group. For example, the preparation of the possible glycine agonist fluorocyclopropane amino acid **151**, was achieved utilising the dimethoxy phenyl compound **150** as a carboxylate synthon.[153]



150 **151**

Substituent groups on the aromatic ring have a profound influence on the rate of oxidation. Electron donating groups are seen to favour the oxidative cleavage of aromatic rings, while electron withdrawing groups will disfavour oxidation.[154] As illustrated with acetate **152**, the addition of a methoxy group to the *para* position of the phenyl ring increases the chemical yield of the acid product **153** from 74% to 82%.[155]

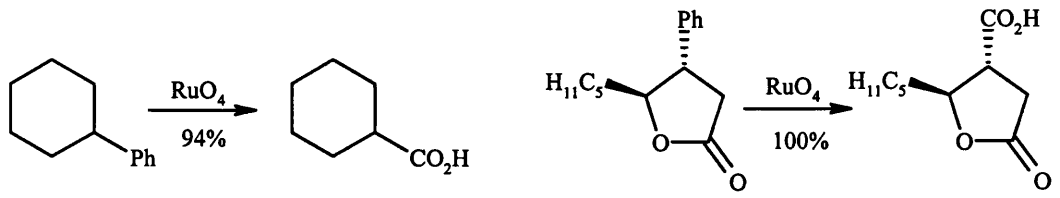


152 **153**

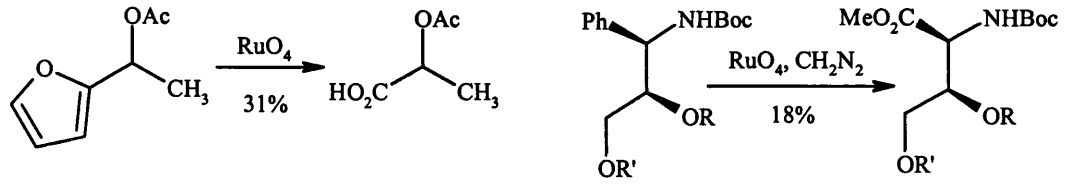
X = H 74%
OMe 82%

The success of ruthenium tetraoxide as an oxidant is marred by its unpredictability. For compounds such as cyclohexylbenzene[137] and the γ-lactone,[156] Scheme 5.3, excellent yields are seen with ruthenium tetraoxide. In contrast, Scheme 5.4 illustrates some poor results with the ruthenium catalyst. The 1-(2-furyl) ethyl acetate[141] affords only 31% of the acid with ruthenium tetraoxide, while treatment of the N-Boc protected amine[157] results in only 18% yield of the N-protected amino ester using this oxidant.

Scheme 5.3



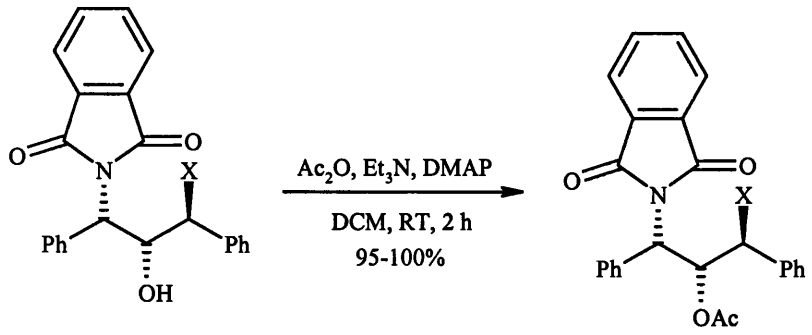
Scheme 5.4



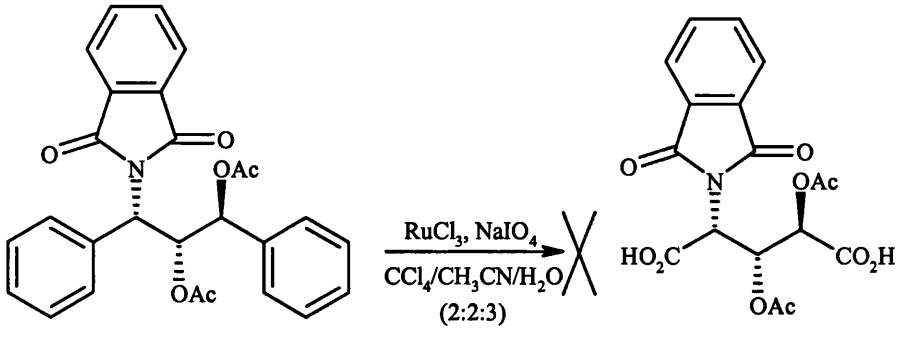
5.2 Oxidation of hydroxy glutamic acid analogues

For the functionalised glutamic acid analogues **128, 138** and **139** (prepared in Chapter 4) the hydroxyl functionality must be first suitably protected before oxidative cleavage. The substrates were acetylated under standard conditions using acetic anhydride, triethylamine with dimethylaminopyridine in

dichloromethane. The products **154, 155** and **156** were identified by methyl singlets of intensity three around δ2 and the loss of the broad OH singlet between δ2-4 in the ^{1}H NMR spectrum, together with the disappearance of the OH stretching at 3200cm^{-1} in the infrared spectrum.

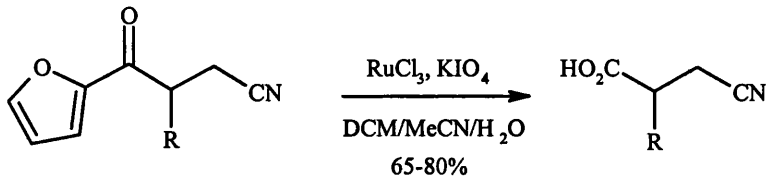


The diacetate **156** was oxidised by treatment with ruthenium tetraoxide under Sharpless conditions[137]($CCl_4/CH_3CN/H_2O$ (2:2:3) and $RuCl_3/NaIO_4$). It is assumed that the phthalimide is unaffected under the reaction conditions due to its electron deficient nature, and only the two phenyl rings are expected to be cleaved.[136,154] After 72 hours of vigorous stirring at room temperature no carboxylic acids were identified. Only starting material was observed by tlc analysis.

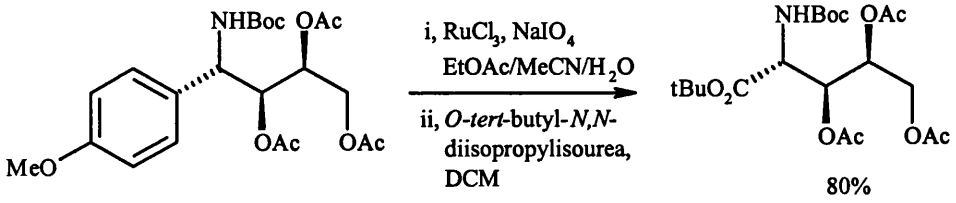


156 **157**

There are cases where better results have been observed when the oxidation has been carried out under modified Sharpless conditions. For example, the oxidation of furylketonitrile **158** to the 2-alkyl-3-cyanopropanoic acid **159** gives better results when dichloromethane is used instead of carbon tetrachloride.[158] The oxidative cleavage of methoxyphenyl **160** to the polyacetoxy amino acid **161** also proceeds with a higher chemical yield when carbon tetrachloride is replaced with ethyl acetate.[159]



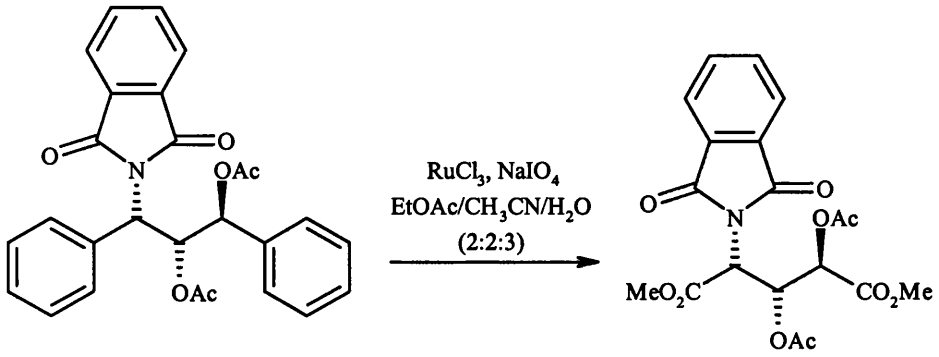
158 **159**



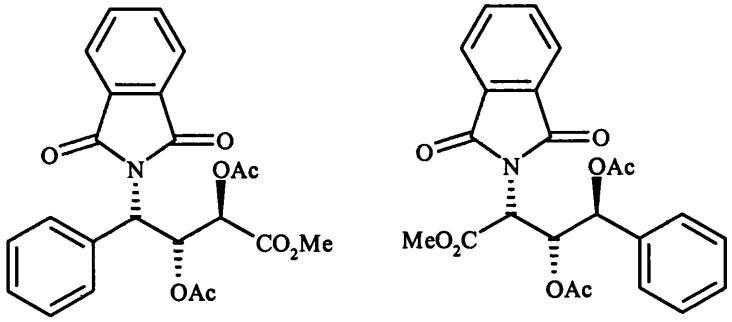
160 **161**

Carbon tetrachloride was replaced with ethyl acetate for the oxidation of diacetate **156**. After 48 hours of stirring at room temperature the ethyl acetate layer turned a pale yellow colour, indicative of excess ruthenium tetraoxide in the reaction mixture. The tlc data suggested the presence of acid functionalities (dark blue staining near the base line using 2.0% w/v 4,4'-bis(dimethylamino)benzhydrol in acetone). Work-up of the mixture gave a light brown paste, which was methylated with diazomethane to give any carboxylic acid products as "chromatography friendly" methyl esters. Purification by silica gel column chromatography gave two fractions. The first fraction was identified as the desired dimethyl ester **162**. The product displayed a molecular ion MH^+ 422.1, and in the ^1H NMR, two singlets at δ3.69 and δ3.73 for the methyl ester groups

together with only 4 protons in the aromatic region for the phthalimide protons. The second fraction (isolated in 28% yield) appeared to be a mixture of compounds. Analysis of the ^1H NMR showed an accumulative total of nine aromatic protons, with two sets of alkyl methine protons, methyl ester singlets and acetate singlets. Correlating this NMR data with an MH^+ ion of 440, we propose the partially oxidised structures **163** and **164** for these compounds.



156 **162** (32%)

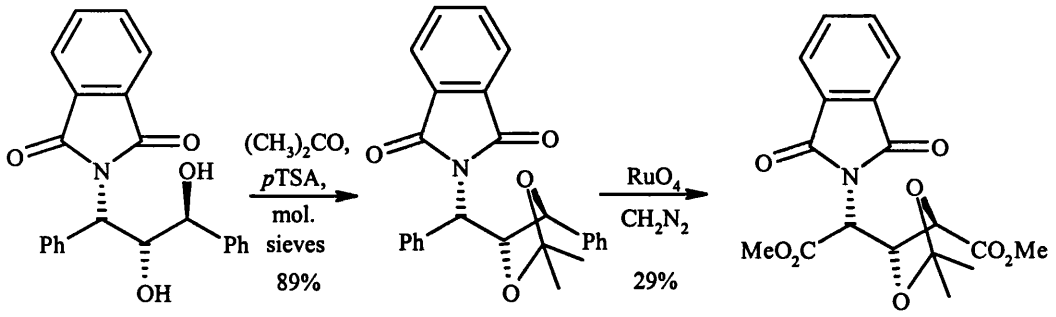


163 **164**

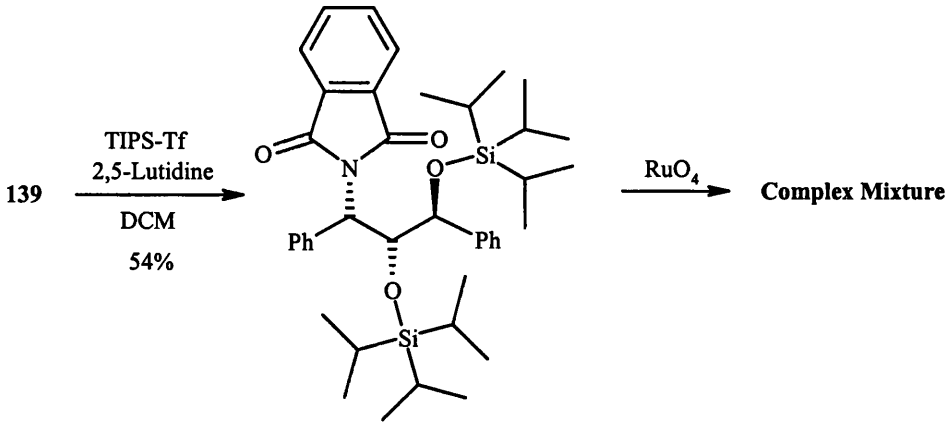
(163 + 164, 28%)

Varying the oxidation conditions; solvent ratios, reaction temperature and co-oxidant (sodium periodate, periodic acid, sodium hypochlorite and tetra-ammonium periodate) failed to enhance the yield, with the maximum yield of diester **162** being only 32%. In investigating the cause of the low yields, the acetate groups came under scrutiny. Even though the acetate protecting group has proven itself previously in ruthenium tetraoxide oxidations,[136,141] we had

reservations about the diacetate moiety. Deprotection of the acetates in the reaction would result in a diol being formed, which would then be cleaved in the presence of ruthenium tetraoxide. Replacement of the acetates with a bridging ketal **165**, however, gave no improvement in the chemical yield (29%) of the diester **166**. Protection with a silicon group[160] (triisopropylsilyl), compound **167**, gave a complex mixture of products. Based on the preliminary results with diacetate **156**, the remaining two hydroxy glutamate analogues were oxidised using the optimum conditions found.



139 **165** **166**

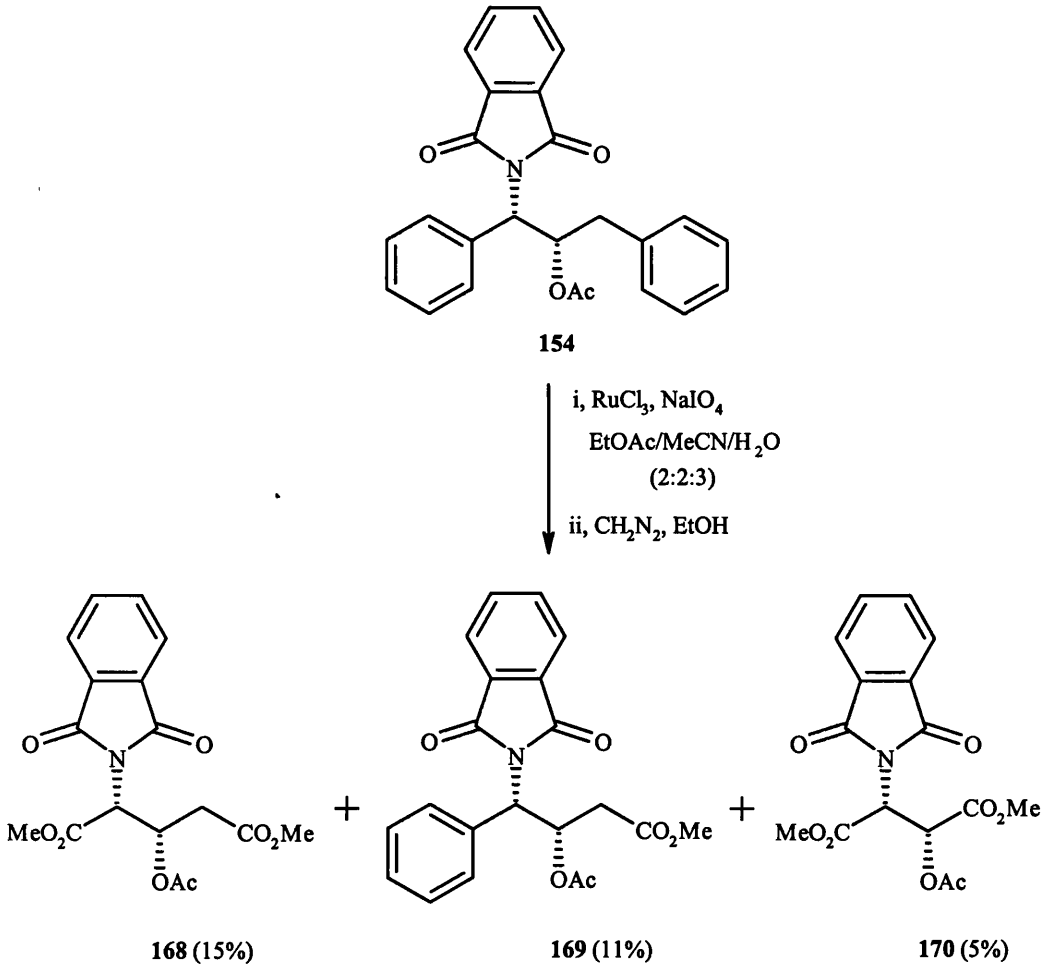


167

Ruthenium oxidation of acetate **154** yielded three products after methylation with diazomethane. The most mobile compound by tlc was in good agreement by ^{1}H NMR with diester **168**, displaying two methyl singlets at δ3.72 and δ3.75 and only phthalimide protons in the aromatic region. The second compound displayed

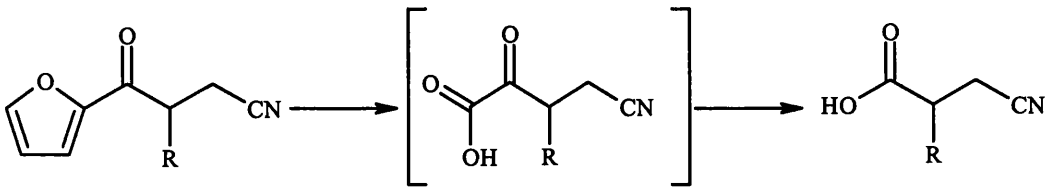
a higher molecular weight than ester **168**, having a high resolution mass spectrum of M^+ 381.1219 and still showed the presence of a phenyl ring in the ^1H NMR. The appearance of only one methyl ester singlet at δ3.63 strongly suggested the partially oxidised compound **169**.

It is interesting to note that oxidation of diacetate **156** with ruthenium tetraoxide gave a mixture of the partially oxidised substrates **163** and **164**, whereas the monoacetate **154** gives only structure **169**. It is speculated that the absence of the electron withdrawing acetate group, next to the right hand phenyl ring in compound **154**, favours the oxidation of the right ring. Whereas, in compound **156** the presence of an electron withdrawing group adjacent to both rings sees little selectivity in the oxidation.



Analysis of the third compound by ^1H NMR showed no characteristic A-B splitting for the CH_2 group, and the representation of proton H_b as a doublet suggested the absence of the methylene unit. The presence of two methyl singlets at δ3.71 and δ3.73 indicated two methyl ester groups and the high resolution mass spectrum M^+ 350.0884 confirmed the compound as diester **170**. This result was surprising, as ruthenium tetraoxide is not expected to oxidise a methylene unit.

Petrini and co-workers have reported a similar transformation. They observed the unexpected formation of carboxylic acid **173** from the oxidation of the furyl derivative **171** with ruthenium tetraoxide. Oxidation of the aromatic compound **171** resulted in the carboxylic acid **173**, presumably *via* the intermediate acid **172**.[158]

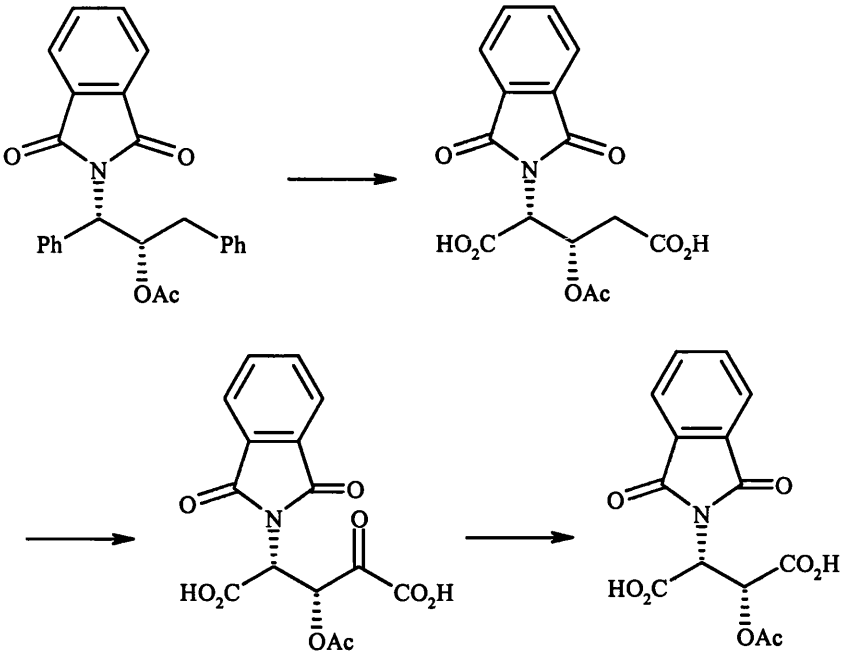


171 **172** **173**

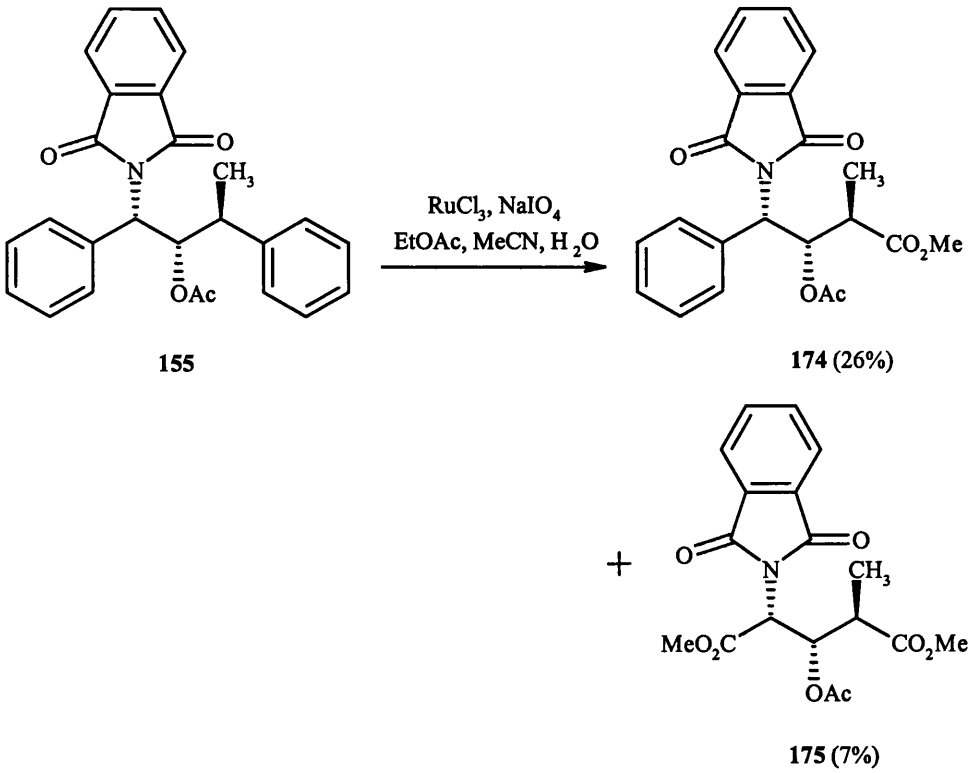
This result may give an explanation as to how the methylene in compound **154** is oxidised (Scheme 5.5). Detection of compounds **169** and **170** together with **168**, would indicate that the reactivity of the intermediate substrates is not ordered, and that the desired diacid product is just one part of the oxidation sequence.

Oxidation of the third analogue, acetate **155**, gave comparable results to the previous two oxidations. A slower reaction was observed with substrate **155**.

Scheme 5.5



Vigorous stirring for 48 hours with ruthenium tetraoxide in ethyl acetate, acetonitrile and water, gave three products. They were the assigned as the partially oxidised mono-phenyl structure **174,** the desired diester **175** and unreacted starting material.



155

174 (26%)

175 (7%)

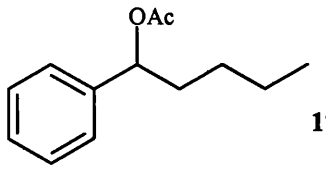
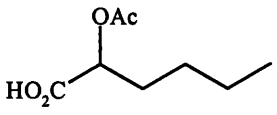
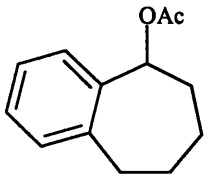
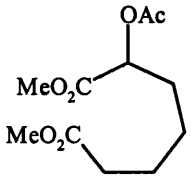
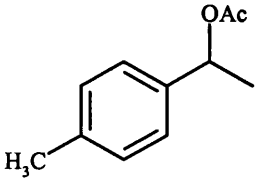
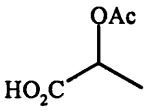
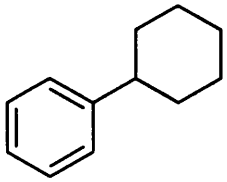
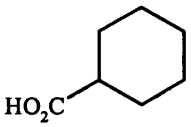
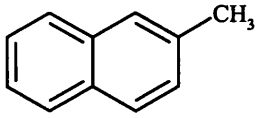
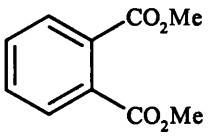
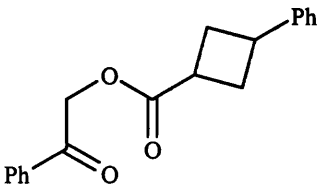
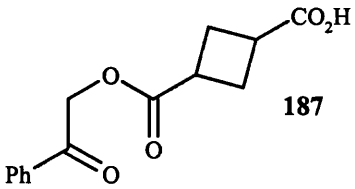
The production of the desired diester compounds by modification of the original solvent system (carbon tetrachloride, acetonitrile and water) was encouraging. Nevertheless, attempts to increase the chemical yields by changing the reaction parameters or by variation of the hydroxyl protecting groups were unsuccessful. Modification of the amine protection and/or activation of the phenyl rings are seen as other alternatives to enhance the yields.

Even though the yields from the oxidations of compounds **162, 168** and **175** are very poor, we thought that the alternative solvent combination (ethyl acetate acetonitrile and water) could be advantageous over the Sharpless system (carbon tetrachloride, acetonitrile and water). Not only because the ethyl acetate solvent system gave the products where carbon tetrachloride failed, but ethyl acetate would be more desirable in terms of the toxicity of the two solvents.

To compare the performance of the two solvent systems, ruthenium tetraoxide oxidations were carried out on a range of aromatic compounds in both solvent systems. The results are shown in Scheme 5.6.

The yields from the reactions show that ethyl acetate can be successfully used as an alternative to carbon tetrachloride in a biphasic solvent system for ruthenium tetraoxide oxidations. The advantage of ethyl acetate in terms of solvent toxicity compared to carbon tetrachloride should be strongly considered, and it is this point that persuades us that ethyl acetate is the progressive choice for ruthenium tetraoxide catalysed transformations.

Scheme 5.6

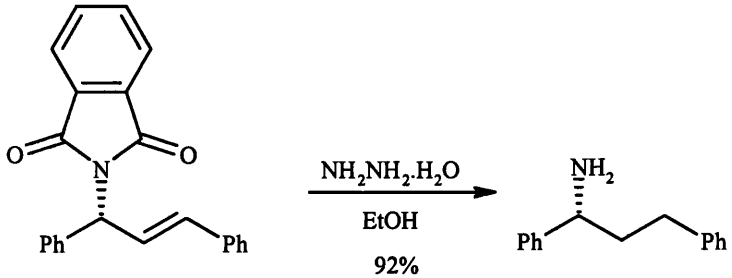
Substrate		Product		Yield (%)	
				EtOAc	*CCl_4*
	**176**		**182**	87	78
	**177**		**183**	66	54
	**178**		**184**	60	40
	**179**		**185**	72	68
	**180**		**186**	43	39
	**181**		**187**	44	50

5.3 Variation of the amine protecting group

Returning to the problem of low yields in the oxidation of aromatic compounds **162, 168** and **175**. Even though phthalimide is an electron withdrawing moiety

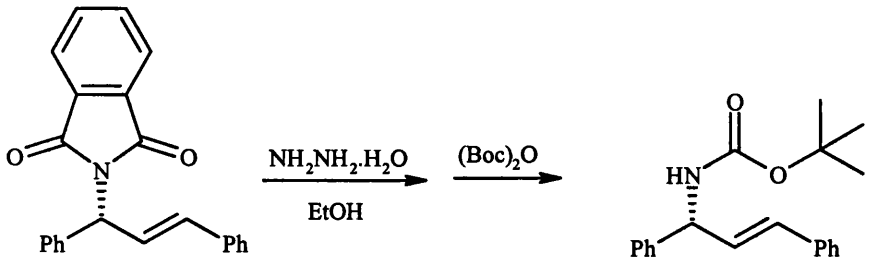
and should not be oxidised in ruthenium catalysed oxidations, to cover all possible areas the phthalimide was replaced with an alternative amine protecting group. There are numerous examples of ruthenium catalysed oxidations on Boc protected amine compounds affording the acid product in good yields.[116,153,159,161] It was shown in Chapter 2, that in the palladium catalysed allylic substitution reaction the *bis*-Boc nucleophile gave low enantioselectivity (54% e.e.), while the best enantioselectivity was seen with the phthalimide nucleophile. If the phthalimide unit in product **92** was to be changed to a Boc group, after the palladium catalysed allylic substitution, the high enantioselectivity from the phthalimide substitution product may be retained in the Boc protected compound.

Deprotection of the phthalimide was achieved by stirring allylic amine **92** with an excess of hydrazine hydrate in ethanol at room temperature for 24 hours.[162] Disappointingly, the deprotection of the phthalimide to the free amine was accompanied by the reduction of the alkene to the saturated derivative **188**. The loss of the olefin peaks, at δ6.71 and δ7.05, in amine **92** were replaced by methylene signals at a higher field (δ1.99 and δ2.59) and the M^+ of 211.1 were consistent with the saturated structure **188.**



92 **188**

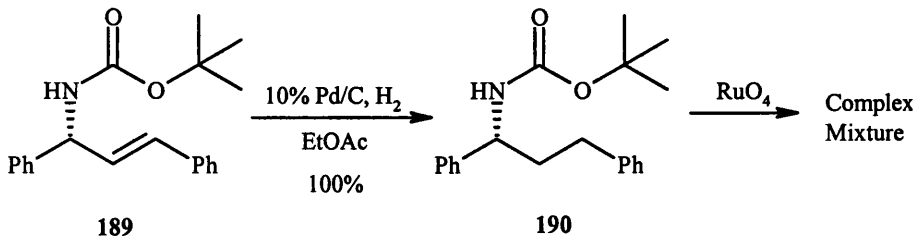
The alkene could be retained in the molecule by using a one-pot procedure of deprotection followed by reprotection. Using hydrazine hydrate and Boc anhydride in the same reaction mixture, the unsaturated Boc protected amine **189** was afforded in a reasonable yield of 69%. From the ^{1}H NMR is was noted that the presence of the bulky Boc group prevented free rotation of the structure, and that two broad signals were observed for the CHN proton. The e.e. of the Boc protected compound could not be resolved by HPLC analysis as the two enantiomers were inseparable on a range of chiral columns.



92 **189**

69%

Putting the question of retention of stereochemistry at the asymmetric centre aside for the moment, the oxidative cleavage of the aromatic rings was the prime interest for the change of N-protection. Therefore, the N-Boc protected allylic amine **189** was smoothly reduced in quantitative yield to the saturated amine **190**.



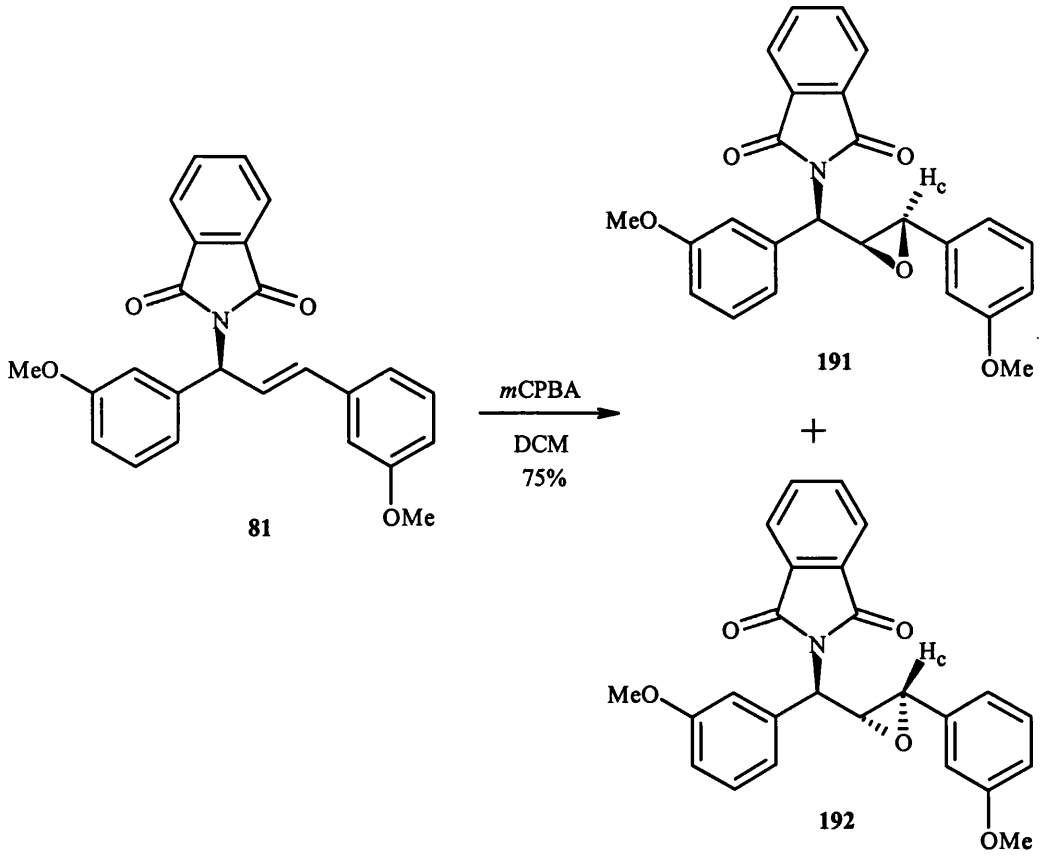
189 **190**

The degradation of the starting substrate **190** to a multitude of compounds with ruthenium tetraoxide dissuaded us from continuing with Boc protection and we decided to return to the phthalimide functionality.

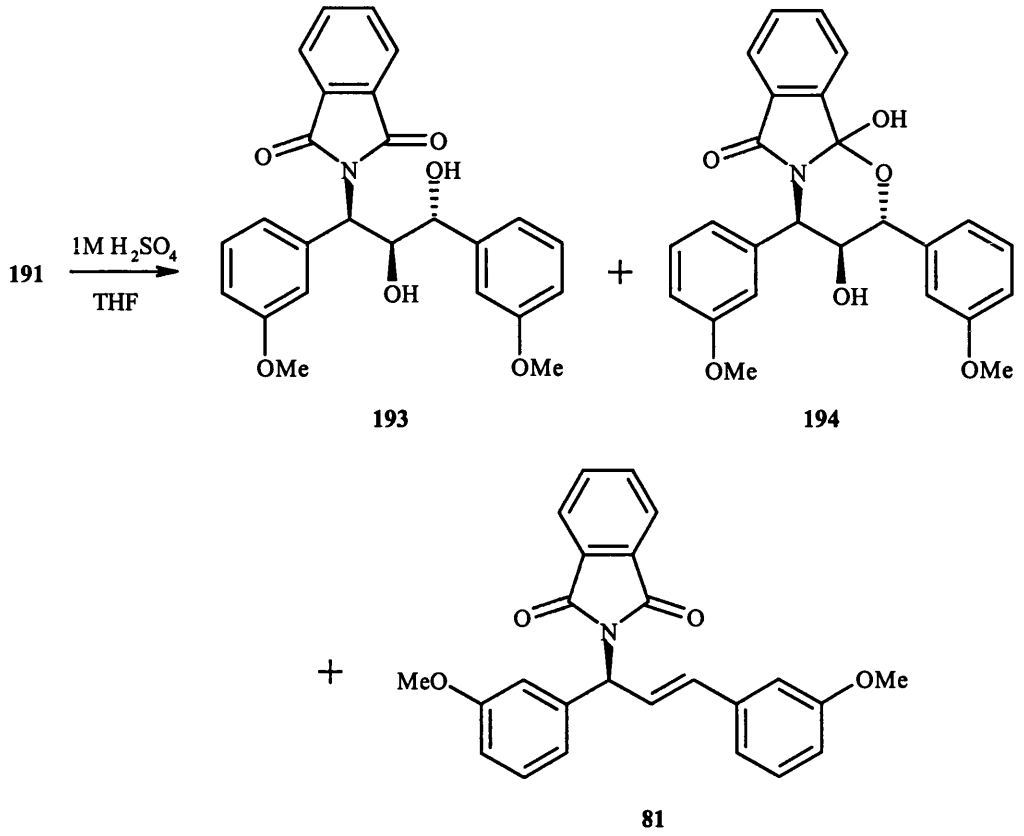
5.4 Oxidation of methoxy phenyl activated substrates

As mentioned in the introduction of this chapter, the phenyl rings can be made more reactive to oxidative cleavage by introducing substituents that donate electron density to the aromatic ring.[136,154] It is hoped that the allylic amines **81** and **82** would give better results in the oxidations, due to the increased activity of the phenyl rings by the inclusion of methoxy substituents. The greater reactivity of the substrates is also anticipated to allow alternative oxidation procedures to be used for a comparison with ruthenium tetraoxide.

Epoxidation of the allylic amine **81** with *m*CPBA was seen to proceed at a much slower rate than with the diphenyl substrate **92**. The diastereomeric ratio of epoxides **191** and **192** was measured using proton NMR (ratio 5:1 **191/192**), utilising the relative intensities of the diastereotopic proton H_c at δ3.86 and δ3.94. The presence of methoxy groups in the structures gave the product as a gummy wax that we were unable to separate by crystallisation. Therefore both diastereoisomers were treated with acid to yield the *trans* diol **193**, which could then be separated by silica gel flash chromatography.

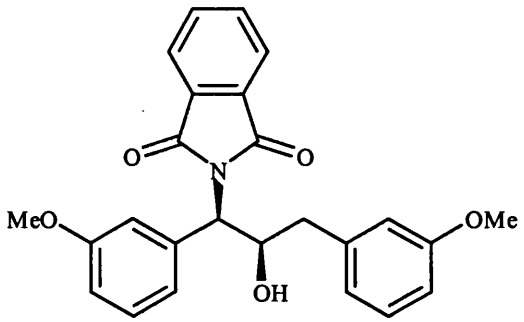


Addition of dilute sulphuric acid to epoxides **191** and **192** in THF gave three products after 24 hours of stirring at room temperature. Two of the products were as expected. The *trans* diol **193** (isolated as the major component in 59% yield) identified by the two OH singlets at δ1.61 and δ2.52 in the ^{1}H NMR and a high resolution mass spectrum of MH^+ 434.1590. The second fraction displayed an MH^+ of 434.1590 and exhibited a similar ^{1}H NMR spectrum to the cyclic ethers **141** and **142**, so the structure **194** was assigned to it. The third fraction, making up 30% of the yield, displayed an identical ^{1}H NMR spectrum to allylic amine **81**, with olefin signals at δ6.69 and δ6.82-7.00, no CHO peaks between δ3-6 and a molecular weight of 399.1. It must be assumed that the increase of electron density to the substrate from the methoxy substituents allows the formation of amine **81**. How the transformation occurs is unclear.



The addition of methoxy groups to the second *meta* position (allylic amine **82**) reduces reactivity of the alkene further. Addition of *m*CPBA to a solution of the alkene **82** in dichloromethane sees only partial conversion of the starting substrate after 24 hours. The formation of a dark purple/ black reaction solution did not seem positive and the reaction was stopped. Work up followed by silica gel chromatography gave the desired epoxide in a poor yield of 9%, with 16% recovered starting material. The low yield observed with the epoxidation of alkene **82,** and the formation of three products from the epoxidation of the methoxy alkene **81,** implies that addition of methoxy substituents to the diphenyl allylic amine is not conducive to the formation of the oxirane rings using peracids.

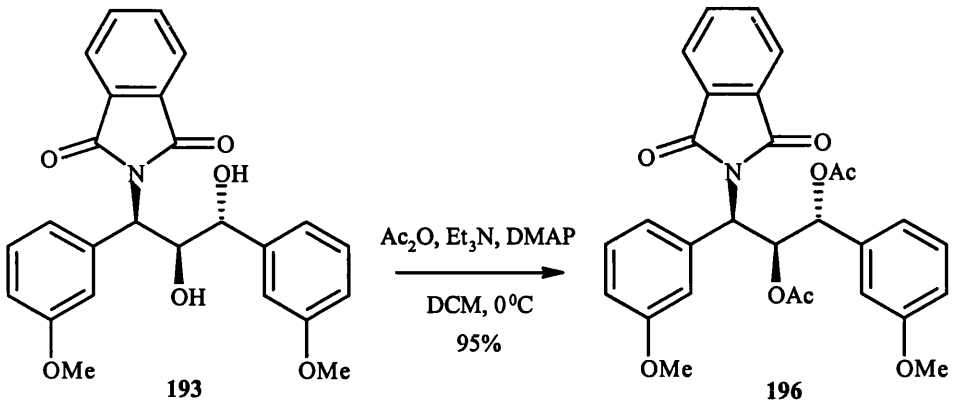
The reduction of the epoxide **191** to the alcohol **195** was also problematic. Hydrogenation with palladium on carbon and hydrogen at atmospheric pressure gave two products by tlc analysis after 72 hours of vigorous stirring. Analysis of the minor product (isolated in 18% yield) showed OH stretching in the infrared spectra at 3467cm^{-1}, and an A-B system of a doublet of doublets (δ2.62 and δ2.80) in the ^{1}H NMR, representative of a CH_2 group in the molecule. The identity of the compound was confirmed as the alcohol **195** by a high resolution mass spectrum of MH^+ 418.1659. Recovered epoxide was the second component of the mixture.



195

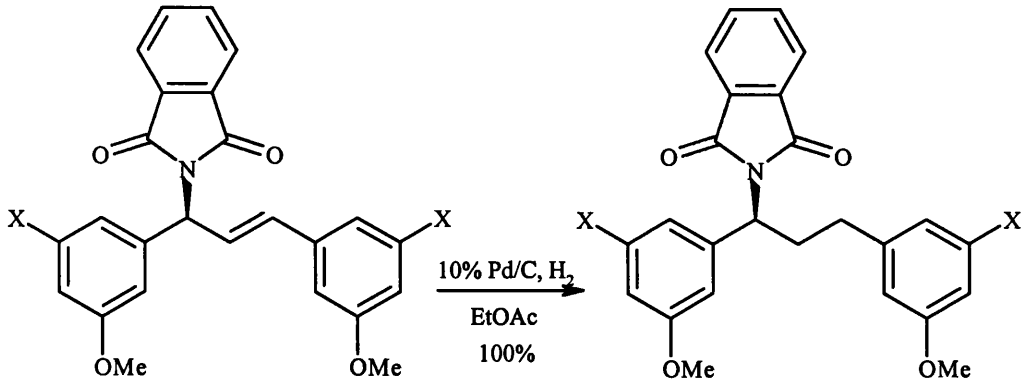
The reason why the reductive cleavage of the epoxide **191** does not proceed with the success seen in the diphenyl epoxide **126**, may be because the methoxy phenyl compound is being perceived as a benzyl ether in the hydrogenation. The addition of the electron donating methoxy substituent will encourage hydrogenation of the benzyl group ahead of the reduction of the epoxide.[163] Degradation of the molecule by hydrogenation, therefore, may be a factor in the poor result. For the dimethoxy analogue this rationale will be amplified, favouring cleavage of the benzyl unit.

The only significant result using the methoxy phenyl derivatives that merited further work was the *trans* diol **193**. Acetylation of the compound was performed under standard conditions of triethylamine, acetic anhydride and DMAP affording the diacetate **196** in 95% yield.



193 **196**

The alkane amine products **197** and **198** were also prepared for the comparison of different oxidation methods. Quantitative yields were achieved for the hydrogenation of alkenes **81** and **82** to alkane derivatives **197** and **198** using 10% palladium on carbon and atmospheric hydrogen.



81 X = H
82 X = OMe

197 X = H
198 X = OMe

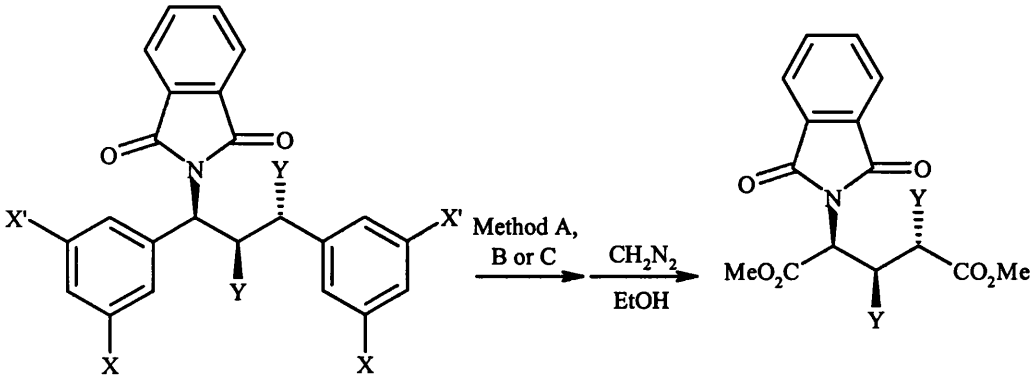
Due to the increased reactivity of the methoxy phenyl rings, two other oxidation procedures were also explored.

The oxidative methods used were:

1) **Method A**: ruthenium tetraoxide generated from $RuCl_3$ and $NaIO_4$ in a biphasic solvent system of ethyl acetate, acetonitrile and water being stirred vigorously at room temperature for 48 hours.

2) **Method B**: ozonolysis in ethyl acetate at room temperature for 3 hours followed by heating to reflux with hydrogen peroxide for 1 hour.[153,164]

3) **Method C**: dry ozonolysis at -78°C with the substrate pre-absorbed on dry silica gel.[165]



159 Y = OAc, X = H, X' = H
196 Y = OAc, X = OMe, X' = H
197 Y = H, X = OMe, X' = H
198 Y = H, X = OMe, X' = OMe

162 Y = OAc
199 Y = H

Method A: $RuCl_3$, $NaIO_4$, $EtOAc/CH_3CN/H_2O$ (2:2:3), 48 h.
Method B: i, O_3, EtOAc, RT, 3 h; ii, H_2O_2, reflux 1 h.
Method C: O_3, SiO_2, -78°C, 5 h.

After each oxidative procedure the carboxylic acid products were derivatised to their methyl esters by treatment with diazomethane before being purified. The purified yields of the methyl esters are shown in Table 5.1.

From these results it is seen that the best oxidation procedures are methods A and B. Both methods give similar results across the range of substrates. The ruthenium tetraoxide has the advantage of being a more vigorous oxidant and is, therefore, able to oxidize a greater range of compounds. The oxidations also

demonstrate that higher yields can be achieved with all the oxidation procedures by addition of extra electron density to the rings.

Table 5.1 Oxidations of aromatic substrates to diester derivatives

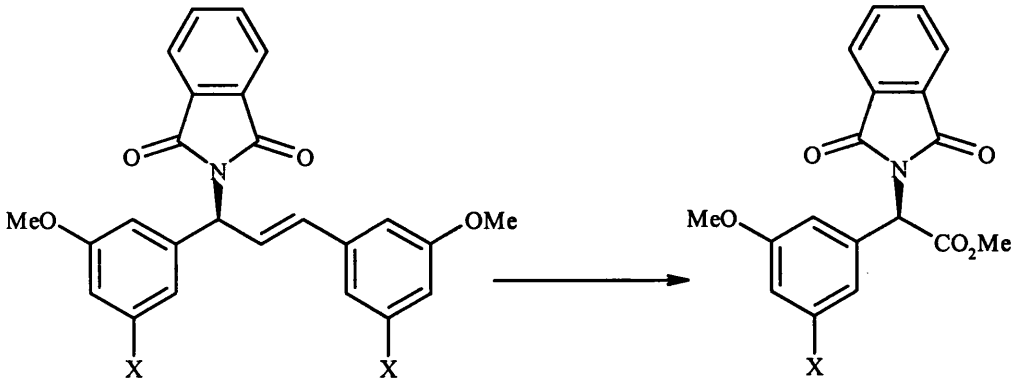
Compound	Oxidation Method	Yield (%)
Diphenyl alkane	A	47
197	A	41
197	B	52
197	C	48
198	A	58
198	B	55
198	C	19
156	A	34
156	C	29
196	A	43
196	B	50
196	C	14

The yields from the methoxy phenyl substrates, are at best, moderate. The problems experienced with the methoxy phenyl substrates in the epoxidation step and subsequent transformations, does not warrant these substrates advantageous in the synthesis of the glutamate analogues.

5.5 Preparation of substituted glycine derivatives

N-Protected glycine derivatives **200** and **201** can be accessed from compounds **81** and **82** by cleavage at the alkene. As discussed in the introduction to this Chapter, ruthenium tetraoxide oxidises many functional groups, with alkenes being cleaved

to carboxylic acids. Alkenes can also be cleaved with ozone, and with an oxidative workup (hydrogen peroxide)[164] carboxylic acids are formed.

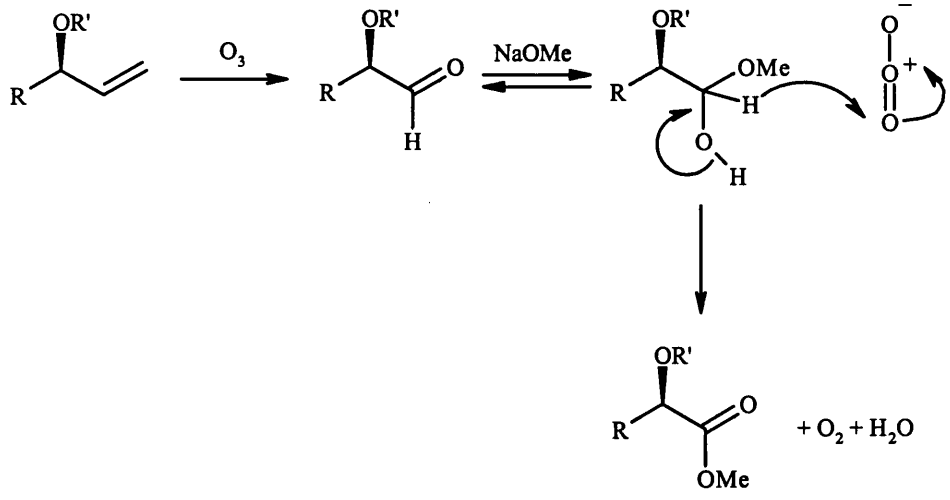


81 X = H
82 X = OMe

200 X = H
201 X = OMe

Marshall *et al* has demonstrated that methyl esters can be accessed directly, if ozonolysis is carried out in a basic medium, such as sodium methoxide.[166] It is suggested by the author that the base in the reaction promotes the formation of a hemiacetal intermediate from the aldehyde and possibly assists in its deprotonation and hydride transfer leading to the ester product (Scheme 5.7). To obtain methyl esters from the ruthenium tetraoxide or ozone/hydrogen peroxide procedures the carboxylic acids must first be methylated.

Scheme 5.7



The yields of the methyl ester **200** from the different oxidation procedures are displayed in Table 5.2. The ruthenium catalysed oxidation was performed in both ethyl acetate and carbon tetrachloride biphasic systems. Both periodic acid and sodium periodate were used as the co-oxidant, exploring the best combinations for the substrate. All ozonolysis reactions were performed at -78°C to prevent further oxidation of the methoxy phenyl rings.

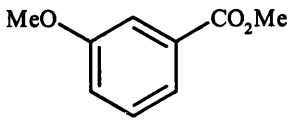
Table 5.2 Yield of methyl ester **200** from the oxidation of alkene **81**.

Substrate	Oxidation method	Yield of 197 (%)
81	RuO_4 (EtOAc/ $NaIO_4$)	20
81	RuO_4 (EtOAc/ H_5IO_6)	26
81	RuO_4 (CCl_4/ $NaIO_4$)	19
81	RuO_4 (CCl_4/ H_5IO_6)	28
81	O_3, NaOMe	32
81	O_3, H_2O_2	56

Oxidation with ruthenium tetraoxide gave a mixture of compounds from alkene **81**. The most polar of the products isolated was identified as the methyl ester **200**. The ^1H NMR analysis showed two methyl singlets at δ3.79 and δ3.81 for the methoxide and the ester methyl groups, and four protons for the methoxy phenyl ring along with the phthalimide protons in the aromatic region. The structure was confirmed as ester **200** by a high resolution MH^+ 326.1040.

The ozonolysis procedures gave cleaner results than the ruthenium catalysed reaction. Ozonolysis in sodium methoxide gave directly the methyl ester **200** in 32% yield together with the methyl ester **202** (62% yield). The best result,

however, was seen with ozone and hydrogen peroxide affording the ester **200** after methylation in 56% yield.



202

Oxidative cleavage of the dimethoxy phenyl alkene **201** did not afford any of the acid product with either the ruthenium catalyst or ozone. It is presumed that the addition of a second methoxy group to the aromatic ring makes the phenyl rings too reactive, and oxidation occurs at all possible cleavage sites.

5.6 Conclusion

We have seen in this chapter that ruthenium tetraoxide can be used to prepare N-protected functionalised glutamic acid analogues from diphenyl precursors, utilising a new solvent combination of ethyl acetate, acetonitrile and water. The low yield in the oxidation products, together with the isolation of over oxidised and partially oxidised side products, prevented this synthetic plan being viable.

The ethyl acetate, acetonitrile and water solvent combination did however, give comparable results to the standard solvent system developed by Sharpless (carbon tetrachloride, acetonitrile and water), and the relative safety of ethyl acetate compared to carbon tetrachloride makes this a good alternative.

N-Protected glycine derivatives have also been prepared from alkene **81** utilising ruthenium tetraoxide. Oxidation of the alkene in compound **81** accesses N-protected α-amino acids. Variation of the aromatic rings in the allylic substrate creates the potential for the synthesis of a range of unnatural amino acids.

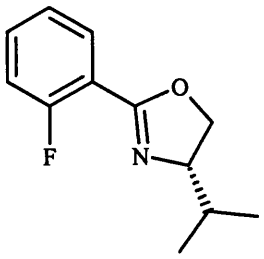
Chapter 6

6 Experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. THF was distilled from sodium benzophenone ketyl under nitrogen prior to use. Ether refers to diethyl ether and light petroleum refers to the petroleum ether fraction collected between 40-60°C.

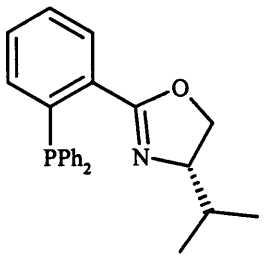
Analytical thin layer chromatography was carried out using glass backed plates coated with Merck Kieselgel 60 GF_{254} or plastic backed plates coated with Merck Kieselgel G/UV_{254}. Plates were visualised under UV light (at 254nm and/or 360nm) or by staining with potassium permanganate or ninhydrin followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Pressure was applied at the column head with hand bellows. Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent.

IR Spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer 1605 FT-IR spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform. Elemental analysis was carried out on a Carlo-Erba Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using Jeol GX270 and Jeol GX400 instruments. High- and low-resolution mass spectra were recorded on a Finnigan MAT 8340 instrument. Optical rotations were carried out on an Optical Activity Ltd. AA-10 Automatic Polarimeter. Mps were measured on an Electrothermal MKII melting point apparatus and were uncorrected.



(4*R*)-2-(2-Fluorophenyl)-4-isopropyl-4,5-dihydro-1,3-oxazole 51.

In a Schlenk flask, zinc chloride (0.551g, 4.045mmol) is melted under high vacuum and cooled under nitrogen. After cooling to room temperature, the *o*-fluorobenzonitrile (8.77cm^3, 80.91mmol) is added under nitrogen followed by (*R*)-(-)-2-amino-3-methyl-1-butanol (10.00g, 97.08mmol). The reaction mixture is heated at 80 °C for 48 hours then allowed to cool to room temperature before being diluted with dichloromethane (150cm^3) and water (200cm^3). The dichloromethane is separated and the aqueous is back-extracted with dichloromethane (100cm^3). The combined organic fractions are washed with water (3x100cm^3) before being dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 80:20) to give the *title compound* as a colourless oil (6.390g, 38%) $[\alpha]_D^{32}$ +60.0 (*c* 2 in $CHCl_3$); ν_{max}/cm^{-1} 1655; δ_H(400MHz; $CDCl_3$) 0.94 (3H, d, *J* 6.7 CH_3), 1.03 (3H, d, *J* 7.0 CH_3), 1.91 (1H, m C*H*$(CH_3)_2$), 4.15 (2H, m CH_2), 4.40 (1H, m CHN), 7.11-7.19 (2H, m Arom H), 7.41-7.46 (1H, m Arom H), 7.88 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 17.90 (CH_3), 18.86 (CH_3), 32.61 (CH), 69.73 (CH_2), 72.60 (CH), 116.70 (Arom CH), 123.88 (Arom CH), 131.15 (Arom CH), 132.59 (Arom CH), 159.19 (C), 160.24 (C), 162.98 (C); *m/z* (CI) 208.1 (MH^+, 100%). Identical to the literature data.[167]



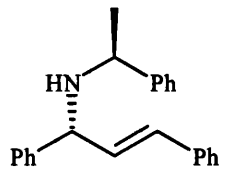
(4*R*)-2-[2-(Diphenylphosphino)phenyl]-4-isopropyl-4,5-dihydro-1,3-oxazole 30a.

To a flame dried flask was added 0.5M solution in THF of potassium diphenylphosphide (96.62cm^3, 48.31mmol) and heated to reflux under an atmosphere of nitrogen. The oxazoline **50** (10.00g, 48.31mmol) in THF (70cm^3) was then added to the refluxing solution and stirred at reflux temperature for 2 hours. The mixture was then transferred to *via* cannular to a separating funnel and partitioned between dichloromethane (250cm^3) and water (250cm^3). The dichloromethane layer was separated and dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a white solid. Recrystallisation from ethyl acetate/hexane gave colourless bricks (9.003g, 85%) mp 86 °C; **30a** $[\alpha]_D^{30}$ -42 (*c* 2 in $CHCl_3$), **ent-30a** $[\alpha]_D^{31}$ +46.0 (*c* 2 in $CHCl_3$) ; ν_{max}/cm^{-1} 1653; δ_H(400MHz; $CDCl_3$) 0.71 (3H, d, *J* 6.7 CH_3), 0.81 (3H, d, *J* 6.7 CH_3), 1.49 (1H, m C*H*$(CH_3)_2$), 3.85 (2H, m CH_2), 4.14 (1H, m CHN), 6.86 (1H, m Arom H), 7.30 (12H, m Arom H), 7.91 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 18.34 (CH_3), 18.89 (CH_3), 32.75 (*C*H$(CH_3)_2$), 70.11 (CH_2), 72.98 (CHN), 128.01 (Arom CH), 128.27 (Arom CH), 128.38 (Arom CH), 128.45 (Arom CH), 128.58 (Arom CH), 128.78 (Arom CH), 129.90 (Arom CH), 130.41 (Arom CH), 131.71 (Arom CH), 131.91 (Arom CH), 133.63 (Arom CH), 133.85

(Arom CH), 134.21 (Arom CH), 134.43 (Arom CH), 137.98 (C), 138.33 (C), 138.75 (C), 139.07 (C), 163.09 (C); *m/z* (CI) 374.2 (MH^+,100%). Identical to literature data.[167]

General procedure (1) for the palladium catalysed allylic substitution of (2*E*)-1,3-diphenyl-2-propenyl acetate 20 with amine nucleophiles.

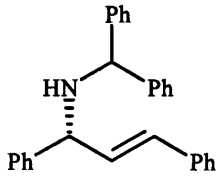
To a solution of (2*E*)-1,3-diphenyl-2-propenyl acetate **20** (0.158mol) in THF ($500cm^3$) was added $[PdCl(C_3H_5)]_2$ (3.95mmol) and ligand **30a** (15.80mmol). The solution was stirred for 10 min after which time the amine (0.272mol) was added. The reaction mixture was then heated under N_2 at 50 °C for 36 hours, after which it was diluted with ether ($300cm^3$) and washed with water ($300cm^3$). The aqueous was back-extracted with ether ($3x200cm^3$) and the combined organic extracts washed with brine ($500cm^3$), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.



***N*-[(1*S*,2*E*)-1,3-Diphenyl-2-propenyl]-*N*-[(1*S*)-1-phenyl]amine 61**

The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a straw coloured oil (0.267g, 86%) (Found: C, 87.9; H, 7.45; N, 4.3. $C_{23}H_{23}N$ requires C, 88.1; H, 7.4; N, 4.5%); (Found, M^+, 313.1826. $C_{23}H_{23}N$ requires M^+, 313.1830); ν_{max}/cm^{-1} 3025 (NH) and 1450; δ_H(270MHz; $CDCl_3$): **61a**, 1.26 (3H,

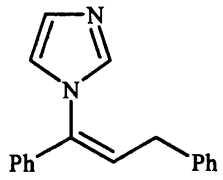
d, *J* 6.6 CH_3), 3.57 (1H, q, *J* 6.6 C*H*CH_3), 4.05 (1H, m CHN), 6.17 (1H, m CH=C*H*Ph), 6.35 (1H, m C*H*=CHPh), 7.10-7.30 (15H, m Arom H): **61b**, 1.31 (3H, d, *J* 6.6 CH_3), 3.87 (1H, q, *J* 6.6 C*H*CH_3), 4.05 (1H, m CHN), 6.16 (1H, m CH=C*H*Ph), 6.35 (1H, m C*H*=CHPh), 7.10-7.30 (15H, m Arom H); δ_C(270MHz; $CDCl_3$): **61a**, 24.42 (CH_3), 54.71 (CH_3*C*HN), 61.96 (CHN), 126.34 (Arom CH), 126.64 (Arom CH), 126.85 (Arom CH), 127.13 (Arom CH), 127.40 (Arom CH), 127.59 (Arom CH), 128.43 (Arom CH), 129.58 (Arom CH), 130.95 (Arom CH), 131.95 (Arom CH), 133.16 (Arom CH), 136.92 (C), 142.81 (C), 145.53 (C): **61a**, 24.63 (CH_3), 55.02 (CH_3*C*HN), 62.15 (CHN), 126.37 (Arom CH), 126.65 (Arom CH), 126.88 (Arom CH), 127.14 (Arom CH), 127.44 (Arom CH), 127.53 (Arom CH), 128.43 (Arom CH), 129.54 (Arom CH), 130.97 (Arom CH), 131.92 (Arom CH), 133.17 (Arom CH), 136.96 (C), 143.35 (C), 145.66 (C); *m/z* (EI) 313.3 (M^+, 6%), 205.2(46), 105.1(100).



(1*S*,2*E*)-*N*-Benzylhydryl-1,3-diphenyl-2-propen-1-amine 62

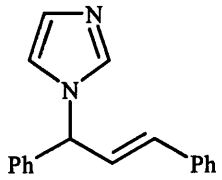
The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a colourless oil (0.310g, 83%) (Found: C, 89.6; H, 6.7; N, 3.4. $C_{28}H_{25}N$ requires C, 89.5; H, 6.7; N, 3.7%); (Found M^+, 375.1985. $C_{28}H_{25}N$ requires M^+, 375.1987); ν_{max}/cm^{-1} 3443 (NH), 3081, 3059 and 3025 (CH); δ_H(270MHz; $CDCl_3$) 1.76 (1H, s NH), 4.20 (1H, d, *J* 7.3 CH=CHC*H*N), 4.80 (1H, s $(Ph)_2$C*H*N), 6.21 (1H, dd, *J*

7.3 and 15.6 PhCH=C*H*), 6.42 (1H, d, *J* 15.6 PhC*H*=CH), 7.10-7.31 (20H, m Arom H); δ_C(270MHz; $CDCl_3$) 61.87 (PhCHN), 63.49 (Ph_2CHN), 126.40 (Arom CH), 126.98 (Arom CH), 127.21 (CH=CH), 127.37 (Arom CH), 127.42 (Arom CH), 127.50 (Arom CH), 127.53 (Arom CH), 128.47 (Arom CH), 128.57 (Arom CH), 130.55 (CH=CH), 132.29 (Arom CH), 136.96 (C), 142.91 (C), 143.82 (C), 143.93 (C); *m/z* (EI) 375.2 (M^+, 13%), 284.1(28), 205.2(27), 193.1(33), 167.1(100); HPLC: 78% e.e.; t_R 13.0/14.4 min [Chiralcel AD, hexane-^{i}PrOH (99:1), 0.5cm^3min^{-1}, 254nm].



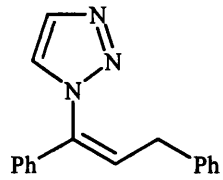
1[(1*Z*)-1,3-diphenyl-1-propenyl]-1*H*-imidazole 63

The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (0.054g, 21%) ν_{max}/cm^{-1} 3113, 3061, 3029, 2921 and 2849 (CH), 1694 and 1598 (C=N-); δ_H(400MHz; $CDCl_3$) 3.33 (2H, d, *J* 6.6 CH_2), 6.29 (1H, t, *J* 6.6 CH=C), 6.90 (1H, s imidazole H), 7.08 (4H, m Arom H), 7.17 (1H, m Arom H), 7.19 (1H, s imidazole H), 7.26 (5H, m Arom H), 7.52 (1H, s imidazole H); δ_C(400MHz; $CDCl_3$) 33.84 (CH_2), 120.36 (Arom CH), 125.57 (Arom CH), 125.76 (C=*C*H), 126.56 (Arom CH), 128.44 (Arom CH), 128.72 (Arom CH), 128.90 (imidazole CH), 129.47 (imidazole CH), 136.01 (C), 136.64 (C), 137.97 (imidazole CH), 138.87 (C); *m/z* (EI) 260.2 (M^+, 7%), 149(15), 122(42), 105(87), 68(100).



1-[(2*E*)-1,3-diphenyl-2-propenyl]-1*H*-imidazole 64

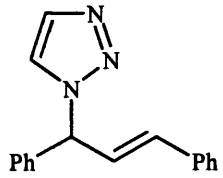
The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (0.039g, 15%) ν_{max}/cm^{-1} 3028 and 2917 (CH), 1719 and 1494 (C=N-); δ_H(400MHz; $CDCl_3$) 5.92 (1H, d, *J* 6.5 CHN), 6.43 (1H, d, *J* 12.0 CH=C*H*Ph), 6.55 (1H, dd, *J* 6.5 and 12.0 C*H*=CHPh), 6.93 (1H, s imidazole H), 7.11 (1H, s imidazole H), 7.20-7.38 (10H, m Arom H), 7.62 (1H, s imidazole H); δ_C(400MHz; $CDCl_3$) 63.45 (CHN), 118.69 (CH), 126.43 (Arom CH), 126.74 (Arom CH), 127.44 (Arom CH), 128.54 (Arom CH), 128.66 (Arom CH), 128.73 (Arom CH), 128.85 (Arom CH), 129.10 (imidazole CH), 134.35 (imidazole CH), 135.48 (C), 136.64 (imidazole CH), 137.91 (C); *m/z* (EI) 260.1 (M^+, 62%), 232.1(24), 193.1(37), 149(100).



1-[(1*Z*)-1,3-diphenyl-1-propenyl]-1*H*-1,2,3 triazole 65

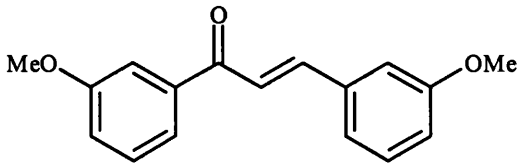
The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column

chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (0.045g, 17%) ν_{max}/cm^{-1} 3061, 3028 and 2920 (CH), 1600 and 1497 (C=N-); δ_H(400MHz; $CDCl_3$) 3.34 (2H, d, *J* 7.3 CH_2), 6.32 (1H, t, *J* 7.3 C=CH), 7.03 (10H, m Arom H), 8.08 (2H, m 2x H triazole); δ_C(400MHz; $CDCl_3$) 33.65 (CH_2), 125.65 (Arom CH), 126.58 (Arom CH), 127.40 (Arom CH), 128.33 (Arom CH), 128.70 (Arom CH), 128.97 (Arom CH), 135.81 (C), 136.01 (C), 138.45 (C), 144.72 (triazole CH), 152.35 (triazole CH); *m/z* (EI) 261.1 (M^+, 12%), 233.1(7), 208.1(6), 191.1(9), 122.0(71), 105.0(100).



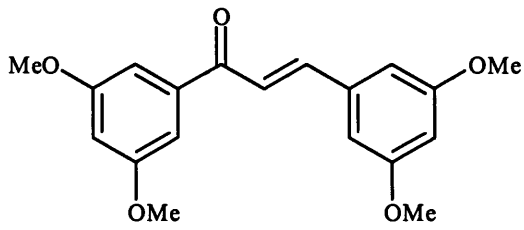
1-[(2*E*)-1,3-diphenyl-2-propenyl]-1*H*-1,2,3 triazole 66

The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (0.060g, 23%) ν_{max}/cm^{-1} 3028 (CH) and 1497 (C=N-); δ_H(400MHz; $CDCl_3$) 6.08 (1H, d, *J* 6.8 CHN), 6.40 (1H, d, *J* 16.1 CH=C*H*Ph), 6.58 (1H, dd, *J* 6.8 and 16.1 CH=CHPh), 7.15-7.32 (10H, m Arom H), 7.92 (1H, m H triazole), 8.03 (1H, m H triazole); δ_C(400MHz; $CDCl_3$) 65.94 (CHN), 125.54 (CH=CH), 126.69 (Arom CH), 127.35 (Arom CH), 128.57 (Arom CH), 128.63 (Arom CH), 128.97 (Arom CH), 134.53 (CH=CH), 135.37 (C), 137.59 (C), 142.58 (triazole CH), 152.05 (triazole CH); *m/z* (EI) 261.1 (M^+, 30%), 223.1(6), 205.1(5), 149(100).



(2*E*)-1,3-bis(3-methoxyphenyl)-2-propen-1-one 71.

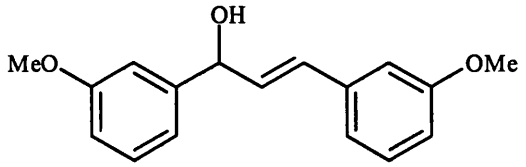
To 3-methoxyacetophenone (5.48cm^3, 40.0mmol) and meta-anisaldehyde (4.87cm^3, 40.0mmol) in methanol (50cm^3) was added NaOH (0.040g, 1.0mmol) and the mixture was stirred at room temperature for 24 hours. Diluted with ether (50cm^3) and water (100cm^3) and the organic fraction separated. The aqueous was back-extracted with ether (3x50cm^3) and the combined ether fractions dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was then purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (8.77g, 82%) ν_{max}/cm^{-1} 2946 and 2840 (CH) and 1666 (C=O); δ_H(270MHz; $CDCl_3$) 3.85 (3H, s OCH_3), 3.87 (3H, s OCH_3), 6.94-7.80 (10H, m CH=CH and Arom H); *m/z* (CI) 269.1 (M^+, 100%).



(2*E*)-1,3-bis(3,5-dimethoxyphenyl)-2-propen-1-one 72.

To 3,5-dimethoxyacetophenone (0.80g, 4.82mmol) and 3,5-dimethoxy benzaldehyde (0.868g, 4.82mmol) in methanol (25cm^3) was added NaOH (0.193g, 4.82mmol) and the mixture was stirred at room temperature for 24 hours.

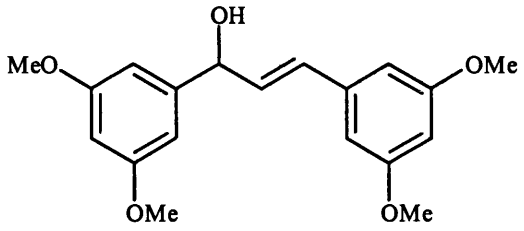
Diluted with ether ($50cm^3$) and water ($100cm^3$) and the organic fraction separated. The aqueous was back-extracted with ether ($3x50cm^3$) and the combined ether fractions dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was then purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (1.210g, 77%) ν_{max}/cm^{-1} 2938 and 2834 (CH) and 1663 (C=O).



(2*E*)-1,3-bis(3-methoxyphenyl)-2-propen-1-ol 73.

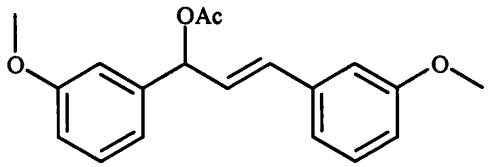
To ketone **71** (2.00g, 7.463mmol) in methanol ($20cm^3$) was added $CeCl_3.H_2O$ (2.78g, 7.463mmol) and stirred at 0 °C for 10 minutes. Sodium borohydride (0.340g, 8.955mmol) was added portion wise maintaining the temperature of the reaction mixture between 0-10 °C followed by stirring at room temperature for 4 hours after addition. Diluted with dichloromethane ($30cm^3$) and water ($50cm^3$) and the organic fraction separated. The aqueous was back-extracted with dichloromethane ($3x30cm^3$) and the combined organic fraction dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a colourless oil (2.00g, 99%) ν_{max}/cm^{-1} 3268 (OH), 3021, 2968 and 2914 (CH); δ_H(270MHz; $CDCl_3$) 1.61 (1H, s OH), 3.78 (3H, s OCH_3), 3.79 (3H, s OCH_3), 5.06 (1H, t, *J* 7.7 CHOH), 6.32 (2H, m CH=CH), 6.40-7.32 (8H, m Arom H); δ_C(270MHz; $CDCl_3$) 55.20 (OCH_3), 79.17 (CHOH), 111.54 (Arom CH),

111.59 (Arom CH), 112.38 (Arom CH), 112.45 (Arom CH), 113.21 (Arom CH), 113.63 (Arom CH), 119.34 (CH=CH), 129.53 (CH=CH), 137.99 (C), 142.70 (C), 159.74 (*C*OCH_3), 159.79 (*C*OCH_3).



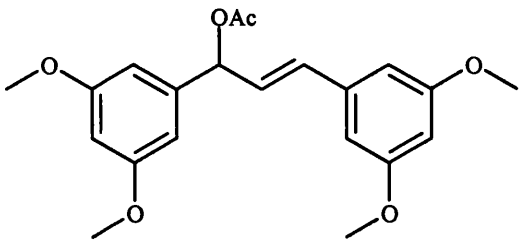
(2*E*)-1,3-bis(3,5-dimethoxyphenyl)-2-propen-1-ol 74.

To ketone **72** (1.210g, 3.69mmol) in methanol (25cm^3) was added $CeCl_3.H_2O$ (1.372g, 3.690mmol) and stirred at 0 °C for 10 minutes. Sodium borohydride (0.168g, 4.428mmol) was added portion wise maintaining the temperature of the reaction mixture between 0-10 °C followed by stirring at room temperature for 4 hours after addition. Diluted with dichloromethane (30cm^3) and water (50cm^3) and the organic fraction separated. The aqueous was back-extracted with dichloromethane (3x30cm^3) and the combined organic fraction dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a colourless oil (1.19g, 98%) ν_{max}/cm^{-1} 3274 (OH), 2961 and 2914 (CH).



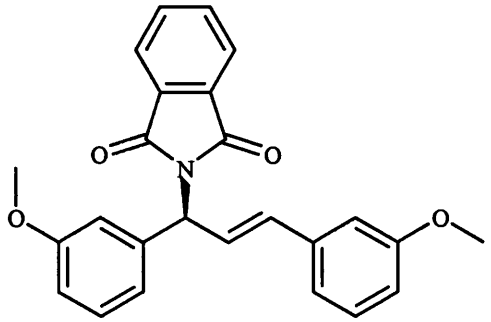
(2*E*)-1,3-bis(3-methoxyphenyl)-2-propenyl acetate 75

To a solution of **73** (16.62g, 61.55mmol) in dichloromethane (150cm^3) was added Et_3N (7.95cm^3, 61.55mmol) and 4-(dimethylamino)pyridine (0.040g) and cooled to 0 °C. Ac_2O (11.60m^3, 123.0mmol) was added and the mixture stirred at room temperature for 2 hours before being diluted with dichloromethane (100cm^3) and saturated sodium hydrogen carbonate (150cm^3) and stirred vigorously for 30 min. The dichloromethane fraction was separated and the aqueous back-extracted with dichloromethane (4x50cm^3). The combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a colourless oil (19.54g, 100%) (Found M^+, 312.1365. $C_{19}H_{20}O_4$ requires M^+, 312.1362); ν_{max}/cm^{-1} 2938 and 2835 (CH), 1736 and 1716 (C=O); δ_H(270MHz; $CDCl_3$) 2.13 (3H, s CH_3), 3.77 (3H, s OCH_3), 3.79 (3H, s OCH_3), 6.29 (1H, d, *J* 6.8 CHO), 6.37 (1H, dd, *J* 6.8 and 15.2 C*H*=CHAr), 6.60 (1H, d, *J* 15.2 CH=C*H*Ar), 6.77-7.00 (6H, m Arom H), 7.17-7.31 (2H, m Arom H); δ_C(270MHz; $CDCl_3$) 21.22 (CH_3), 55.09 (2xOCH_3), 75.84 (CHO), 111.72 (Arom CH), 112.61 (Arom CH), 113.32 (Arom CH), 113.79 (Arom CH), 119.18 (Arom CH), 119.26 (Arom CH), 127.56 (HC=CH), 129.44 (Arom CH), 129.61 (Arom CH), 132.41 (CH=CH), 137.47 (C), 140.67 (C), 159.67 (C), 169.87 (C=O); *m/z* (FAB+) 312.1 (M^+, 20%), 270.1(12), 253.1(100).



(2*E*)-1,3-bis(3,5-dimethoxyphenyl)-2-propenyl acetate 76

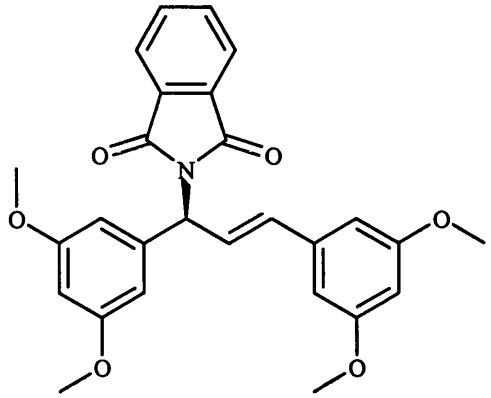
To a solution of **72** (8.74g, 26.485mmol) in dichloromethane (70cm^3) was added Et_3N (3.59cm^3, 27.81mmol) and 4-(dimethylamino)pyridine (0.020g) and cooled to 0 °C. Ac_2O (4.99m^3, 52.97mmol) was added and the mixture stirred at room temperature for 2 hours before being diluted with dichloromethane (50cm^3) and saturated sodium hydrogen carbonate (70cm^3) and stirred vigorously for 30 min. The dichloromethane fraction was separated and the aqueous back-extracted with dichloromethane (4x20cm^3). The combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a colourless oil (9.36g, 95%) (Found M^+, 372.1577. $C_{21}H_{24}O_6$ requires M^+, 372.1573); ν_{max}/cm^{-1} 3001, 2937 and 2838 (CH), 1736 (C=O); δ_H(270MHz; $CDCl_3$) 2.14 (3H, s CH_3), 3.77 (6H, s 2xOCH_3), 3.79 (6H, s 2xOCH_3), 6.26-6.41 (4H, m C*H*O, C*H*=CHAr, CH=C*H*Ar and Arom H), 6.52-7.59 (5H, m Arom H); δ_C(270MHz; $CDCl_3$) 21.27 (CH_3), 55.30 (4xOCH_3), 75.88 (CHO), 99.83 (Arom CH), 100.48 (Arom CH), 104.68 (Arom CH), 104.94 (Arom CH), 127.69 (CH=CH), 132.61 (CH=CH), 138.09 (C), 141.46 (C), 160.84 (2x$COCH_3$), 160.92 (2x$COCH_3$), 169.91 (C=O); *m/z* (EI) 372.2 (M^+, 12%), 149(44), 121(100).



(1*S*,2*E*)-1-Phthaloyl-1,3-bis(3-methoxyphenyl)-2-propene 81.

To (2*E*)-1,3-bis(3-methoxyphenyl)-2-propenyl acetate **75** (19.20g, 62.0mmol) in THF ($200cm^3$) was added $[PdCl(C_3H_5)]_2$ (0.284g, 0.775mmol) and phosphinooxazoline ligand **ent-30a** (1.156g, 3.10mmol). The solution was stirred for 10 minutes after which potassium phthalimide (18.31g, 99.20mmol) was added. The reaction mixture was heated under nitrogen at 50 °C for 72 hours, after which it was diluted with ether (150 cm^3) and washed with water ($200cm^3$). The aqueous was back-extracted with ether ($50cm^3$x4) and the combined organic fractions were dried ($MgSO_4$) was evaporated *in vacuo* to the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a cream gum (21.61g, 88%) $[\alpha]_D^{27}$ +16.0 (*c* 2 in $CHCl_3$); (Found M^+, 399.1469. $C_{25}H_{21}NO_4$ requires M^+, 399.1470); ν_{max}/cm^{-1} 3055, 3000, 2939 and 2834 (CH), 1771 and 1710 (NC=O); δ_H(270MHz; $CDCl_3$) 3.75 (3H, s OCH_3), 3.78 (3H, s OCH_3), 6.06 (1H, d, *J* 8.61 CHN), 6.66 (1H, d, *J* 15.9 C*H*=CHAr), 6.78 (2H, m CH=C*H*Ar and Arom H), 6.87-7.06 (5H, m Arom H), 7.17-7.26 (2H, m Arom H), 7.68 (2H, dd, *J* 2.9 and 5.3 Arom H), 7.81 (2H, dd, *J* 2.9 and 5.3 Arom H); δ_C(270MHz; $CDCl_3$) 55.57 (2xOCH_3), 56.68 (CHN), 111.99 (Arom CH), 113.09 (Arom CH), 113.58 (Arom CH), 114.16 (Arom CH), 119.64 (Arom CH), 119.81 (Arom CH), 123.60 (Arom CH), 125.54 (CH=CH), 129.75 (Arom CH), 129.84 (Arom CH), 131.98 (C),

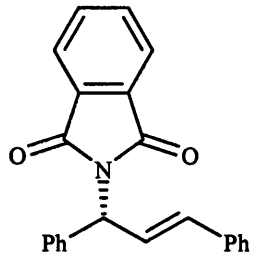
134.35 (Arom CH), 134.58 (CH=CH), 137.74 (C), 140.47 (C), 159.82 (2x$COCH_3$), 169.24 (NC=O); *m/z* (FAB+) 399.2 (M^+, 100%); HPLC 92% e.e.; t_R 31/33.5 min [Chiracel AD, hexane-Pr^iOH (75:25), 0.75cm^3min^{-1}; 254nm].



(1*S*,2*E*)-1-Phthaloyl-1,3-bis(3,5-dimethoxyphenyl)-2-propene 82

To (2*E*)-1,3-bis(3,5-dimethoxyphenyl)-2-propenyl acetate **76** (9.65g, 25.94 mmol) in THF (100cm^3) was added $[PdCl(C_3H_5)]_2$ (0.119g, 0.324mmol) and phosphinooxazoline ligand **ent-30a** (0.484g, 1.297mmol). The solution was stirred for 10 minutes after which potassium phthalimide (9.60g, 51.88mmol) was added. The reaction mixture was heated under nitrogen to 50 °C for 96 hours, after which it was diluted with ether (100 cm^3) and washed with water (150cm^3). The aqueous was back-extracted with ether (30cm^3x4) and the combined organic fractions were dried ($MgSO_4$) was evaporated *in vacuo* to the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 6:4) to give the *title compound* as a cream gum (7.74g, 65%) $[\alpha]_D^{31}$ +13.5 (*c* 2 in $CHCl_3$); (Found M^+, 459.1674. $C_{27}H_{25}NO_6$ requires M^+, 459.1681); ν_{max}/cm^{-1} 3000, 2934 and 2838 (CH), 1771 and 1712 (NC=O); δ_H(270MHz; $CDCl_3$) 3.76 (6H, s 2xOCH_3), 3.78 (6H, s 2xOCH_3), 6.02 (1H, d, *J* 8.6 CHN), 6.38 (2H, s Arom H), 6.58 (2H, m Arom H), 6.62-6.66 (1H, m

CH=C*H*Ar), 6.99 (1H, dd, *J* 8.6 and 15.75 C*H*=CHAr), 7.71 (2H, m Arom H), 7.83 (2H, m Arom H); δ_C(270MHz; $CDCl_3$) 55.33 (4xOCH_3), 56.43 (CHN), 99.34 (Arom CH), 100.50 (Arom CH), 104.73 (Arom CH), 105.64 (Arom CH), 123.36 (CH=CH), 125.57 (Arom CH), 131.93 (C), 134.02 (CH=CH), 134.51 (Arom CH), 138.17 (C), 141.14 (C), 160.89 (2x$COCH_3$), 160.92 (2x$COCH_3$), 167.67 (NC=O); *m/z* (FAB+) 460.2 (MH^+, 47%), 279(69) and 53(100); HPLC 93% e.e.; t_R 11.5/13.0 min [Chiracel OD, hexane-Pr^{i}OH (70:30), 1cm^{3}min^{-1}; 254nm].



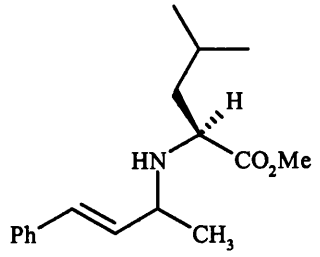
(1*R*,2*E*)-1-Phthaloyl-1,3-diphenyl-2-propene 92

The general procedure (1) for the palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a colourless crystalline solid (48.71g, 91%) mp 102°C; (Found: C, 81.3; H, 5.1; N, 4.2. $C_{23}H_{17}NO_2$ requires C, 81.4; H, 5.1; N, 4.1%); **92** $[\alpha]_D^{30}$ –20.0 (*c* 2 in $CHCl_3$), **ent-92** $[\alpha]_D^{32}$ +21.0 (*c* 2 in $CHCl_3$); (Found MH^+, 339.1257. $C_{23}H_{17}NO_2$ requires MH^+, 339.1259); ν_{max}/cm^{-1} 3058 and 3026 (CH), 1770 and 1709 (NC=O); δ_H(400MHz; $CHCl_3$) 6.13 (1H, d, *J* 8.4 ArCHN), 6.71 (1H, d, *J* 16.0 ArC*H*=CH), 7.05 (1H, dd, *J* 8.4 and 16.0 ArCH=C*H*) and 7.20-7.90 (14H, m Arom H); δ_C(400MHz; $CHCl_3$) 56.43 (CHN), 123.41 (Arom CH), 125.35 (CH=CH), 126.75 (Arom CH), 127.42 (Arom CH), 127.73 (Arom CH), 128.17

(Arom CH), 128.65 (Arom CH), 132.01 (C), 134.02 (CH=CH), 136.21 (C), 138.94 (C), 167.88 (NC=O); *m/z* (EI) 339.1 (M^+, 17%) and 192(100); HPLC: 96% e.e.; t_R 15(**ent-92**)/18(**92**) min [Chiralcel OD, hexane-^{i}PrOH (99:1), 1cm^{3}min^{-1}, 254nm].

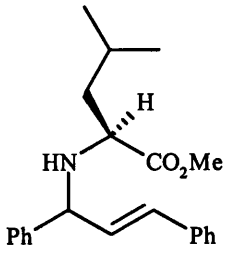
General procedure (2) for the preparation of the allylic amino esters.

(2*E*)-1,3-diphenyl-2-propenyl acetate **20** (0.250g, 0.992mmol), $[PdCl(C_3H_5)]_2$ (0.009g, 0.020mmol) and diphenylphosphino ethane (0.040g, 0.099mmol) was stirred in dry THF (4cm^3) for 30 min at room temperature before addition of *L*-amino ester **98** (1.98mmol) as a solution in THF (5cm^3). The mixture was stirred at room temperature for 18 hours followed by heating at reflux for 24 hours under nitrogen. (The reaction mixture on occasions needed further amounts of catalyst (0.009g, 0.020mmol) and ligand (0.040g, 0.099mmol) for complete consumption of starting material.) The mixture was diluted with ether (20cm^3) and washed with water (30cm^3). The aqueous was back-extracted with ether (3x25cm^3) and the combined organic fractions washed with saturated brine (100cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.



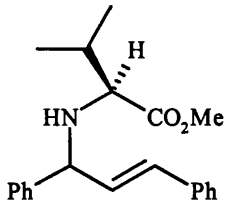
Methyl-(2*S*)-2-{[(2*E*)-1-methyl-3-phenyl-2-propenyl]amino}-4-methyl pentanoate 97

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give the *title compound* as a yellow oil (0.250g, 69%) δ_H(400MHz; $CDCl_3$) 0.90 (6H, m 2xCH_3), 0.90 (1H, m C*H*(CH_3)$_2$), 1.22 (3H, dd, *J* 0.6 and 6.1 CHNC*H*$_3$), 1.43 (2H, m CH_2), 1.75 (1H, m PhCHN), 3.30 (1H, m C*H*CO_2Me), 3.52 (3H, s CO_2CH_3), 3.72 (3H, s CO_2CH_3), 5.98 (1H, dd, *J* 7.9 and 15.9 C*H*=CHPh), 6.02 (1H, dd, *J* 8.2 and 15.9 C*H*=CHPh), 6.44 (1H, d, *J* 15.9 CH=C*H*Ph), 6.45 (1H, d, *J* 15.9 CH=C*H*Ph), 7.12-7.41 (5H, m Arom H); δ_C(400MHz; $CDCl_3$) 21.40 (*C*H_3CH), 22.06 (*C*H_3CH), 22.35 (CH_3CHN), 22.36 (CH_3CHN), 22.55 (CH), 24.78 (CHCO_2Me), 24.82 (CHCO_2Me), 43.15 (CH_2), 51.58 (CO_2CH_3), 54.87 (CHN), 55.67 (CHN), 57.26 (CHN), 57.72 (CHN), 126.23 (Arom CH), 127.29 (Arom CH), 128.44 (Arom CH), 129.71 (CH=CH), 130.43 (CH=CH), 133.60 (CH=CH), 134.21 (CH=CH), 136.91 (C), 177.07 (C).



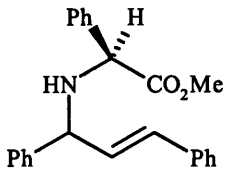
Methyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-4-methylpentanoate 99a and 100a.

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99a** and **100a** as a straw coloured oil (0.230g, 69%) (Found M^+, 337.2035. $C_{22}H_{27}NO_2$ requires M^+, 337.2042); ν_{max}/cm^{-1} 1735 (C=O); δ_H(400MHz; $CDCl_3$): **99a**, 0.67-0.90 (6H, m 2xCH_3), 1.34-1.40 (2H, m CH_2), 1.78 (1H, m C*H*$(CH_3)_2$), 3.07 (1H, dd, *J* 5.8 and 8.6 C*H*CO_2Me), 3.57 (3H, s CO_2CH_3), 4.22 (1H, d, *J* 7.7 CHN), 6.19 (1H, dd, *J* 7.7 and 15.75 C*H*=CHPh), 6.46 (1H, d, *J* 15.7 CH=C*H*Ph), 7.10-7.33 (10H, m Arom H): **100a**, 0.67-0.90 (6H, m 2xCH_3), 1.34-1.40 (2H, m CH_2), 1.78 (1H, m $CH(CH_3)_2$), 3.42 (1H, dd, *J* 5.9 and 8.45 $CHCO_2$Me), 3.61 (3H, s CO_2CH_3), 4.22 (1H, d, *J* 7.7 CHN), 6.15 (1H, dd, *J* 7.7 and 15.75 C*H*=CHPh), 6.51 (1H, d, *J* 15.75 CH=C*H*Ph), 7.10-7.33 (10H, m Arom H); δ_C(400MHz; $CDCl_3$) **99a** and **100a**, 21.82 (CH_3), 22.91 (CH_3), 24.67 (CH), 43.25 (CH_2), 51.63 (CH_3), 57.15 (CHN), 64.25 (CHN), 126.44 (Arom CH), 127.02 (Arom CH), 127.42 (Arom CH), 127.57 (Arom CH), 128.49 (Arom CH), 128.51 (Arom CH), 132.66 (Arom CH), 136.89 (C), 142.17 (C), 176.90 (CO_2Me); *m/z* (EI) 337.3 (M^+, 15%), 294.2(32), 208(38), 193.1(49), 149.1(100).



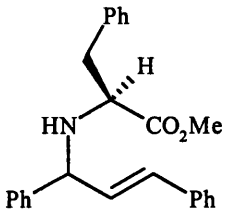
Methyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-3-methylbutanoate 99b and 100b.

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99b** and **100b** as a straw coloured oil (0.232g, 72%) ν_{max}/cm^{-1} 1738 (C=O); δ_H(270MHz; $CDCl_3$): **99b**, 0.88 (6H, m 2xCH_3), 1.85 (1H, m $CH(CH_3)_2$), 2.84 (1H, d, *J* 5.8 C*H*CO_2Me), 3.59 (3H, s CH_3), 4.18 (1H, d, *J* 7.7 CHN), 6.19 (1H, m C*H*=CHPh), 6.42 (1H, m CH=C*H*Ph), 7.11-7.33 (10H, m Arom H): **100b** 0.88 (6H, m 2xCH_3), 1.85 (1H, m $CH(CH_3)_2$), 3.18 (1H, d, *J* 5.8 C*H*CO_2Me), 3.63 (3H, s CO_2CH_3), 4.18 (1H, d, *J* 7.7 CHN), 6.16 (1H, m C*H*=CHPh), 6.47 (1H, m CH=C*H*Ph), 7.11-7.33 (10H, m Arom H); δ_C(270MHz; $CDCl_3$) **99b** and **100b**, 18.50 (CH_3), 19.39 (CH_3), 31.80 (CH), 51.40 (CO_2CH_3), 64.35 (CHN), 64.51 (CHN), 126.43 (Arom CH), 127.32 (Arom CH), 127.46 (Arom CH), 127.61 (Arom CH), 128.44 (Arom CH), 128.47 (Arom CH), 128.57 (Arom CH), 130.14 (Arom CH), 132.78 (Arom CH), 136.84 (C), 142.17 (C), 176.10 (CO_2Me); *m/z* (CI) 324.4 (MH^+, 100%).



Methyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}(phenyl) acetate 99c and 100c

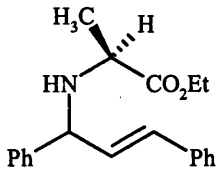
The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99c** and **100c** as a colourless oil (0.234g, 68%) (Found M^+, 357.1728. $C_{24}H_{23}NO_2$ requires M^+, 357.1729); ν_{max}/cm^{-1} 2920 (CH) and 1735 (C=O); δ_H(400MHz; $CDCl_3$): **99c**, 1.56 (1H, s NH), 3.66 (3H, s CO_2CH_3), 4.28 (1H, d, *J* 7.8 CHN), 4.45 (1H, s $CHCO_2Me$), 6.27 (1H, dd, *J* 8.3 and 15.6 C*H*=CHPh), 6.51 (1H, d, *J* 16.1 CH=C*H*Ph), 7.18-7.42 (15H, m Arom H): **100c**, 2.56 (1H, s NH), 3.67 (3H, s CO_2CH_3), 4.26 (1H, d, *J* 7.3 CHN), 4.40 (1H, s $CHCO_2Me$), 6.30 (1H, dd, *J* 7.3 and 17.1 C*H*=CHPh), 6.55 (1H, d, *J* 17.1 CH=C*H*Ph), 7.18-7.42 (15H, m Arom H); δ_C(400MHz; $CDCl_3$): **99c** and **100c**, 52.24 (CH_3), 62.53 (CHN), 126.49 (Arom CH), 127.38 (Arom CH), 127.49 (Arom CH), 127.55 (Arom CH), 128.13 (Arom CH), 128.53 (Arom CH), 128.64 (Arom CH), 128.71 (Arom CH), 128.75 (Arom CH), 131.14 (Arom CH), 131.57 (Arom CH), 136.67 (C), 138.16 (C), 142.17 (C), 173.64 (CO_2Me); *m/z* (FAB+) 358.2 (MH^+, 24%), 193.1(100); HPLC: 46% d.e.; t_R=37/ 56 min [Chiracel OJ, Hexane/^{i}PrOH 99:1, 0.5cm^3min^{-1}; 254nm].



Methyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-3-phenylpropanoate 99d and 100d

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99d** and **100d** as a straw coloured oil (0.270g, 74%) (Found: C, 80.7; H, 6.9; N, 3.9. $C_{25}H_{25}NO_2$ requires C, 80.8; H, 6.8; N, 3.8%); (Found MH^+, 372.1971. $C_{25}H_{25}NO_2$ requires MH^+, 372.1966); ν_{max}/cm^{-1} 3325 and 2950 (CH), 1735 (C=O); δ_H(270MHz; $CDCl_3$): **99d**, 2.93 (2H, dd, *J* 7.15 and 12.6 CH_2Ph), 3.41 (1H, t, *J* 7.3 $CHCO_2Me$), 3.60 (3H, s CH_3), 4.31 (1H, d, *J* 7.15 CHN), 6.23 (1H, dd, *J* 7.5 and 15.75 C*H*=CHPh), 6.47 (1H, d, *J* 15.75 CH=C*H*Ph), 7.12-7.37 (15H, m Arom H): **100d**, 2.97 (2H, m CH_2Ph), 3.70 (1H, t, *J* 6.8 $CHCO_2Me$), 3.63 (3H, s CH_3), 4.29 (1H, d, *J* 6.0 CHN), 6.07 (1H, dd, *J* 7.5 and 15.9 C*H*=CHPh), 6.43 (1H, d, *J* 15.7 CH=C*H*Ph), 7.12-7.37 (15H, m Arom H); δ_C(270MHz; $CDCl_3$): **99d**, 40.01 (CH_2), 51.62 (CH_3), 60.12 (CHN), 63.78 (CHN), 126.47 (Arom CH), 127.28 (Arom CH), 127.35 (Arom CH), 128.29 (Arom CH), 128.44 (Arom CH), 128.44 (Arom CH), 129.33 (Arom CH), 130.28 (Arom CH), 130.76 (Arom CH), 131.45 (Arom CH), 132.40 (Arom CH), 136.75 (C), 137.30 (C), 141.85 (C), 175.14 (CO_2Me): **100d**, 40.05 (CH_2), 51.62 (CH_3), 60.31 (CHN), 64.03 (CHN), 126.62 (Arom CH), 127.324 (Arom CH), 127.37 (Arom CH), 128.22 (Arom CH), 128.48 (Arom CH), 128.57 (Arom CH), 129.33 (Arom CH), 130.22 (Arom CH),

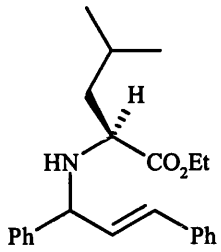
130.75 (Arom CH), 131.48 (Arom CH), 132.49 (Arom CH), 136.76 (C), 137.44 (C), 142.73 (C), 175.34 (CO_2Me); *m/z* (FAB+) 372.2 (MH^+, 19%), 193.1(100).



Methyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}propanoate 99e and 100e.

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99e** and **100e** as a straw coloured oil (0.171g, 56%) (Found M^+, 309.1720. $C_{20}H_{23}NO_2$ requires M^+, 309.1729); ν_{max}/cm^{-1} 3026 and 2950 (CH), 1730 (C=O); δ_H(400MHz; $CDCl_3$): **99e**, 1.17 (6H, m CH_2CH_3 and CH_3), 3.15 (1H, q, *J* 7.1 $CHCO_2Et$), 4.08 (2H, m CH_2CH_3), 4.25 (1H, d, *J* 6.05 CHN), 6.20 (1H, dd, *J* 7.7 and 15.8 CH=CHPh), 6.44 (1H, d, *J* 6.6 CH=CHPh), 7.10-7.30 (10H, m Arom H): **100e**, 1.17 (6H, m CH_2CH_3 and CH_3), 3.42 (1H, q, *J* 7.15 $CHCO_2Et$), 4.08 (2H, m CH_2), 4.27 (1H, d, *J* 7.3 CHN), 6.20 (1H, dd, *J* 7.7 and 15.8 CH=CHPh), 6.49 (1H, d, *J* 6.8 CH=CHPh), 7.10-7.30 (10H, m Arom H); δ_C(400MHz; $CDCl_3$): **99e**, 14.21 (CH_3), 19.37 (CH_3), 53.97 (CHN), 60.65 (CH_2), 63.64 (CHN), 126.44 (Arom CH), 127.39 (Arom CH), 128.47 (Arom CH), 128.58 (Arom CH), 130.24 (Arom CH), 130.83 (Arom CH), 131.54 (Arom CH), 132.34 (Arom CH), 136.71 (C), 142.12 (C), 175.90 (CO_2Et): **100e**, 14.21 (CH_3), 19.64 (CH_3), 54.23 (CHN), 60.65 (CH_2), 63.93 (CHN), 126.46 (Arom CH), 127.48 (Arom CH), 128.47 (Arom CH), 128.56 (Arom CH), 130.28 (Arom CH), 130.80 (Arom CH), 131.50

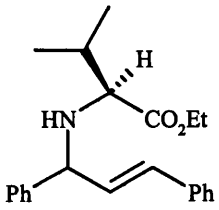
(Arom CH), 132.39 (Arom CH), 136.85 (C), 142.74 (C), 176.16 (CO_2Et); *m/z* (CI) 310.1 (MH^+, 100%).



Ethyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-4-methylpentanoate 99f and 100f.

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99f** and **100f** as a straw coloured oil (0.244g, 70%) (Found M^+, 351.2184. $C_{23}H_{29}NO_2$ requires M^+, 351.2198); ν_{max}/cm^{-1} 2956 (CH), 1730 (C=O); δ_H(270MHz; $CDCl_3$): **99f**, 0.77-0.95 (6H, m $CH(CH_3)_2$), 1.28 (3H, m CH_2CH_3), 1.46 (1H, m $CH(CH_3)_2$), 1.90 (2H, m $CH_2CH(CH_3)_2$), 3.13 (1H, dd, *J* 5.8 and 8.6 $CHCO_2Et$), 4.15 (2H, m $CO_2CH_2CH_3$), 4.32 (1H, d, *J* 7.5 CHN), 6.28 (1H, dd, *J* 7.7 and 15.9 CH=CHPh), 6.55 (1H, d, *J* 15.9 CH=CHPh), 7.20-7.45 (10H, m Arom H): **100f**, 0.77-0.95 (6H, m $CH(CH_3)_2$), 1.28 (3H, m CH_2CH_3), 1.46 (1H, m $CH(CH_3)_2$), 1.90 (2H, m $CH_2CH(CH_3)_2$), 3.48 (1H, t, *J* 7.1 $CHCO_2Et$), 4.15 (2H, m $CO_2CH_2CH_3$), 4.30 (1H, d, *J* 7.5 CHN), 6.23 (1H, dd, *J* 7.7 and 15.9 CH=CHPh), 6.60 (1H, d, *J* 15.95 CH=CHPh), 7.20-7.45 (10H, m Arom H); δ_C(270MHz, $CDCl_3$): **99f**, 14.26 (CH_3), 21.96 (CH_3), 22.94 (CH), 24.66 (CH_3), 43.03 (CH_2), 57.17 (CHN), 60.46 (CH_2), 63.93 (CHN), 126.44 (Arom CH), 127.35 (Arom CH), 127.44 (Arom CH), 128.46 (Arom CH), 128.58 (Arom CH), 130.99 (Arom CH), 131.77 (Arom CH), 132.75 (Arom CH), 136.84 (C), 142.25 (C), 176.42 (CO_2Et):

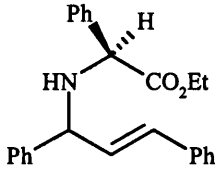
100f, 14.36 (CH_3), 22.15 (CH_3), 22.94 (CH), 24.84 (CH_3), 43.23 (CH_2), 57.42 (CHN), 60.47 (CH_2), 64.15 (CHN), 126.43 (Arom CH), 127.32 (Arom CH), 127.55 (Arom CH), 128.46 (Arom CH), 130.15 (Arom CH), 130.94 (Arom CH), 131.78 (Arom CH), 132.77 (Arom CH), 136.96 (C), 142.25 (C), 176.42 (CO_2Et); *m/z* (CI) 352.1 (MH^+, 100%).



Ethyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-3-methylbutanoate 99g and 100g.

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99g** and **100g** as a straw coloured oil (0.190g, 57%) (Found M^+, 337.2032. $C_{22}H_{27}NO_2$ requires M^+, 337.2042); ν_{max}/cm^{-1} 3025 and 2965 (CH), 1730 (C=O); δ_H(400MHz; $CDCl_3$): **99g**, 0.95 (6H, m $CH(CH_3)_2$), 1.24 (3H, m CH_2CH_3), 1.93 (1H, m $CH(CH_3)_2$), 2.90 (1H, d, *J* 6.05 $CHCO_2Et$), 4.18 (2H, q, *J* 6.9 $CO_2CH_2CH_3$), 4.27 (1H, d, *J* 7.7 CHN), 6.30 (1H, dd, *J* 7.7 and 15.75 CH=CHPh), 6.54 (1H, d, *J* 15.75 CH=CHPh), 7.2-7.46 (10H, m Arom H): **100g**, 0.95 (6H, m $CH(CH_3)_2$), 1.24 (3H, m CH_2CH_3), 1.93 (1H, m $CH(CH_3)_2$), 3.24 (1H, d, *J* 5.8 $CHCO_2Et$), 4.18 (2H, q, *J* 6.9 $CO_2CH_2CH_3$), 4.27 (1H, d, *J* 7.7 CHN), 6.23 (1H, dd, *J* 7.7 and 15.75 CH=CHPh), 6.61 (1H, d, *J* 15.75 CH=CHPh), 7.20-7.46 (10H, m Arom H); δ_C(400MHz; $CDCl_3$): **99g**, 14.31 (CH_3), 18.41 (CH_3), 19.43 (CH), 30.82 (CH_3), 60.37 (CH_2), 64.32 (CHN), 64.46

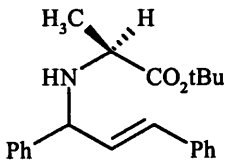
(CHN), 126.38 (Arom CH), 127.23 (Arom CH), 127.43 (Arom CH), 128.46 (Arom CH), 130.05 (Arom CH), 130.85 (Arom CH), 132.05 (Arom CH), 132.82 (Arom CH), 136.85 (C), 142.26 (C), 175.55 (CO_2Et): **100g**, 14.31 (CH_3), 18.52 (CH_3), 19.44 (CH), 31.75 (CH_3), 60.39 (CH_2), 64.39 (CHN), 64.46 (CHN), 126.38 (Arom CH), 127.32 (Arom CH), 127.63 (Arom CH), 128.51 (Arom CH), 130.03 (Arom CH), 130.81 (Arom CH), 132.07 (Arom CH), 132.88 (Arom CH), 136.95 (C), 143.36 (C), 175.56 (CO_2Et); *m/z* (CI) 338.1 (MH^+, 100%).



Ethyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}(phenyl)acetate 99h and 100h

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99h** and **100h** as a straw coloured oil (0.093g, 26%) (Found MH^+, 372.1977. $C_{25}H_{25}NO_2$ requires MH^+, 372.1965); ν_{max}/cm^{-1} 1732 (C=O); δ_H(400MHz; $CDCl_3$): **99h**, 1.20 (3H, m CH_2CH_3), 4.10 (2H, m CH_2CH_3), 4.25 (1H, d, *J* 8.3 CHN), 4.37 (1H, s $CHCO_2Et$), 6.27 (1H, m CH=CHPh), 6.49 (1H, d, *J* 15.6 CH=CHPh), 7.16-7.39 (15H, m Arom H): **100h**, 1.20 (3H, m CH_2CH_3), 4.10 (2H, m CH_2CH_3), 4.25 (1H, d, *J* 8.3 CHN), 4.37 (1H, s $CHCO_2Et$), 6.27 (1H, m CH=CHPh), 6.54 (1H, d, *J* 16.1 CH=CHPh), 7.16-7.39 (15H, m Arom H); δ_C(400MHz; $CDCl_3$): **99h**, 14.02 (CH_3), 61.16 (CH_2), 62.37 (CHN), 62.66 (CHN), 126.45 (Arom CH), 127.39 (Arom CH), 127.58 (Arom CH), 127.99 (Arom CH), 128.57 (Arom CH), 128.79 (Arom CH), 128.85 (Arom CH), 130.54 (Arom CH), 131.03 (Arom CH), 131.73

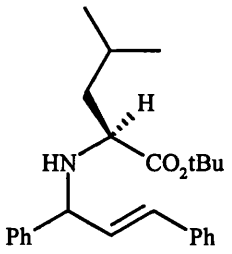
(Arom CH), 131.95 (Arom CH), 136.72 (C), 138.13 (C), 142.13 (C), 173.01 (CO_2Et): **100h**, 14.16 (CH_3), 60.34 (CH_2), 62.56 (CHN), 62.83 (CHN), 126.42 (Arom CH), 127.41 (Arom CH), 127.54 (Arom CH), 127.93 (Arom CH), 128.67 (Arom CH), 128.77 (Arom CH), 128.89 (Arom CH), 130.50 (Arom CH), 131.05 (Arom CH), 131.79 (Arom CH), 131.93 (Arom CH), 136.82 (C), 138.20 (C), 142.19 (C), 173.10 (CO_2Et); *m/z* (FAB+) 372.2 (MH^+, 18%), 193.1(100).



***tert*Butyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}propanoate 99i and 100i.**

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99i** and **100i** as a straw coloured oil (0.150g, 45%) (Found M^+, 337.2039. $C_{22}H_{27}NO_2$ requires M^+, 337.2042); ν_{max}/cm^{-1} 2926 (CH), 1722 (C=O); δ_H(400MHz; $CDCl_3$): **99i**, 1.25 (3H, d, *J* 7.3 CHC*H*$_3$), 1.45 (9H, s C(C*H*$_3$)$_3$), 3.11 (1H, q, *J* 7.3 C*H*CH$_3$), 4.38 (1H, d, *J* 7.8 CHN), 6.28 (1H, dd, *J* 7.8 and 15.6 C*H*=CHPh), 6.54 (1H, d, *J* 15.6 CH=C*H*Ph), 7.18-7.42 (10H, m Arom H): **100i**, 1.28 (3H, d, *J* 7.3 CHC*H*$_3$), 1.48 (9H, s C(C*H*$_3$)$_3$), 3.39 (1H, q, *J* 6.8 C*H*CH$_3$), 4.35 (1H, d, *J* 7.8 CHN), 6.27 (1H, dd, *J* 7.8 and 16.1 C*H*=CHPh), 6.57 (1H, d, *J* 15.6 CH=C*H*Ph), 7.18-7.42 (10H, m Arom H): δ_C(400MHz; $CDCl_3$): **99i**, 19.32 (CH_3), 28.00 (CH_3), 54.49 (CHN), 63.64 (CHN), 80.88 (C), 126.46 (Arom CH), 127.39 (Arom CH), 127.49 (Arom CH), 128.44 (Arom CH), 130.16 (Arom CH), 130.81 (Arom CH), 131.62 (Arom CH), 132.61 (Arom CH), 136.83 (C), 142.23 (C), 175.23 (CO_2Bu^t): **100i**,

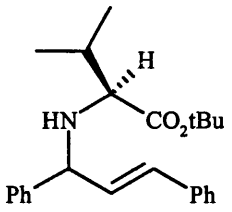
19.68 (CH_3), 28.18 (CH_3), 54.87 (CHN), 63.86 (CHN), 80.86 (C), 126.45 (Arom CH), 127.48 (Arom CH), 127.52 (Arom CH), 128.43 (Arom CH), 130.13 (Arom CH), 130.86 (Arom CH), 131.62 (Arom CH), 132.64 (Arom CH), 136.81 (C), 142.82 (C), 175.45 (CO_2Bu^t); *m/z* (CI) 338.1 (MH^+, 100%).



***tert*Butyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-4-methylpentanoate 99j and 100j.**

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99j** and **100j** as a straw coloured oil (0.298g, 80%) ν_{max}/cm^{-1} 3026 and 2960 (CH), 1725 (C=O); δ_H(270MHz; $CDCl_3$): **99j**, 0.90 (6H, m 2xCH_3), 1.48 (2H, m CH_2), 1.52 (9H, s C(C*H*$_3$)$_3$), 1.93 (1H, m C*H*(CH_3)$_2$), 3.04 (1H, dd, *J* 5.8 and 8.3 C*H*CO_2Bu^t), 4.40 (1H, d, *J* 6.8 CHN), 6.30 (1H, m C*H*=CHPh), 6.58 (1H, d, *J* 15.6 CH=C*H*Ph), 7.20-7.50 (10H, m Arom H): **100j**, 0.90 (6H, m 2xCH_3), 1.48 (2H, m CH_2), 1.56 (9H, s C(C*H*$_3$)$_3$), 1.93 (1H, m C*H*(CH_3)$_2$), 3.43 (1H, t *J* 7.3 $CHCO_2Bu^t$), 4.38 (1H, d, *J* 7.3 CHN), 6.30 (1H, m C*H*=CHPh), 6.65 (1H, d, *J* 16.1 CH=C*H*Ph), 7.20-7.50 (10H, m Arom H); δ_C(270MHz; $CDCl_3$): **99j**, 21.93 (CH_3), 22.83 (CH_3), 24.72 (CH), 28.16 (CH_3), 43.04 (CH_2), 57.63 (CHN), 63.85 (CHN), 80.67 (C), 126.47 (CH), 127.29 (CH), 128.30 (CH), 128.46 (CH), 129.99 (CH), 130.86 (CH), 131.83 (CH), 132.95 (CH), 136.94 (C), 142.33 (C), 175.55 (CO_2Bu^t): **100j**, 22.34 (CH_3), 22.95 (CH_3), 24.87 (CH), 28.19 (CH_3), 43.25 (CH_2),

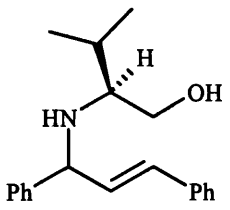
58.00 (CHN), 64.09 (CHN), 80.60 (C), 126.45 (CH), 127.34 (CH), 128.41 (CH), 128.52 (CH), 129.92 (CH), 131.35 (CH), 132.14 (CH), 132.83 (CH), 137.44 (C), 143.15 (C), 175.68 (CO_2Bu^t); *m/z* (CI) 380.3 (MH^+, 17%), 193(100).



***tert*Butyl-(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-3-methylbutanoate 99k and 100k.**

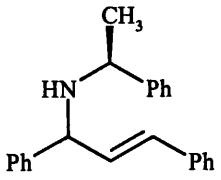
The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 8:2) to give a mixture of **99k** and **100k** as a straw coloured oil (0.257g, 71%); ν_{max}/cm^{-1} 3026 and 2966 (CH), 1722 (C=O); δ_H(400MHz; $CDCl_3$): **99k**, 0.95 (6H, m 2xCH_3), 1.48 (9H, s $C(CH_3)_3$), 1.89 (1H, m $CH(CH_3)_2$), 2.76 (1H, d, *J* 5.6 $CHCO_2Bu^t$), 4.29 (1H, d, *J* 7.5 CHN), 6.27 (1H, m CH=CHPh), 6.55 (1H, m CH=CHPh), 7.14-7.43 (10H, m Arom H): **100k**, 0.95 (6H, m 2xCH_3), 1.51 (9H, m $C(CH_3)_3$), 1.89 (1H, m $CH(CH_3)_2$), 3.11 (1H, d, *J* 5.8 $CHCO_2Bu^t$), 4.29 (1H, d, *J* 7.5 CHN), 6.27 (1H, m CH=CHPh), 6.55 (1H, m CH=CHPh), 7.14-7.43 (10H, m Arom H); δ_C(400MHz; $CDCl_3$): **99k**, 18.32 (CH_3), 19.43 (CH_3), 28.12 (CH_3), 31.75 (CH), 55.16 (CHN), 64.14 (CHN), 80.73 (C), 126.17 (CH), 126.47 (CH), 127.30 (CH), 128.40 (CH), 129.86 (CH), 131.38 (CH), 132.15 (CH), 133.13 (CH), 136.98 (C), 142.49 (C), 174.76 (CO_2Bu^t): **100k**, 18.56 (CH_3), 19.45 (CH_3), 28.24 (CH_3), 31.71 (CH), 55.23 (CHN), 64.46 (CHN), 80.77 (C), 126.49 (CH), 127.20 (CH), 127.38 (CH), 128.40

(CH), 129.84 (CH), 131.85 (CH), 132.16 (CH), 133.18 (CH), 136.99 (C), 142.48 (C), 174.79 (CO_2Bu^t); *m/z* (CI) 366.2 (MH^+, 15%), 193.1(100).



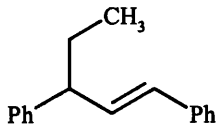
(2*S*)-2-{[(2*E*)-1,3-diphenyl-2-propenyl]amino}-3-methyl-1-butanol 99l and 100l

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether8:2) to give a mixture of **99l** and **100l** as a straw coloured oil (0.248g, 85%) (Found MH^+, 296.2010. $C_{20}H_{26}NO$ requires MH^+, 296.2013); ν_{max}/cm^{-1} 3260 (OH) and 2958 (CH); δ_H(270MHz; $CDCl_3$): **99l**, 0.85 (6H, m 2xCH_3), 1.84 (1H, m C*H*(CH_3)$_2$), 1.98 (1H, s OH), 2.42 (1H, m C*H*CH_2OH), 3.31 (1H, dd, *J* 2.2 and 10.6 C*H*$_2$OH), 3.57 (1H, dd, *J* 4.4 and 10.6 C*H*$_2$OH), 4.42 (1H, d, *J* 5.5 CHN), 6.20 (1H, m C*H*=CHPh), 6.45 (1H, d, *J* 2.9 CH=C*H*Ph), 7.12-7.35 (10H, m Arom H): **100l**, 0.85 (6H, m 2xCH_3), 1.84 (1H, m C*H*(CH_3)$_2$), 1.98 (1H, s OH), 2.44 (1H, m C*H*CH_2OH), 3.29 (1H, dd, *J* 2.2 and 10.6 C*H*$_2$OH), 3.45 (1H, dd, *J* 4.4 and 10.6 C*H*$_2$OH), 4.42 (1H, d, *J* 5.5 CHN), 6.20 (1H, m C*H*=CHPh), 6.51 (1H, d, *J* 2.7 CH=C*H*Ph), 7.12-7.35 (10H, m Arom H); δ_C(270MHz; $CDCl_3$): **99l** and **100l**, 14.12 (CH_3), 18.11 (CH_3), 28.79 (CH), 60.38 (CH_2), 60.77 (CHN), 62.89 (CHN), 126.36 (CH), 127.18 (CH), 127.34 (CH), 127.55 (CH), 128.42 (CH), 128.72 (CH), 130.31 (CH), 132.46 (CH), 136.68 (C), 142.75 (C); *m/z* (FAB+) 296.2 (MH^+, 19%), 193.1(100).



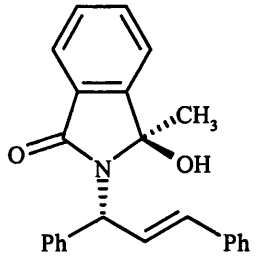
_N_-[(2_E_)-1,3-Diphenyl-2-propenyl]-_N_-[(1_S_)-1-phenyl]amine 99m and 100m

The general procedure (2) for the preparation of the allylic amino esters was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether8:2) to give a mixture of **99m** and **100m** as a straw coloured oil (0.267g, 86%) (Found M^+, 313.1826. $C_{23}H_{23}N$ requires M^+, 313.1830); ν_{max}/cm^{-1} 3025 (CH); δ_H(270MHz; $CDCl_3$): **99m**, 1.26 (3H, d, *J* 6.6 CH_3), 3.57 (1H, q, *J* 6.6 NC*H*CH_3), 4.05 (1H, m CHN), 6.17 (1H, m CH=CHPh), 6.35 (1H, m CH=CHPh), 7.10-7.30 (15H, m Arom H): **100m**, 1.31 (3H, d, *J* 6.6 CH_3), 3.87 (1H, q, *J* 6.6 NC*H*CH_3), 4.05 (1H, m CHN), 6.16 (1H, m CH=CHPh), 6.35 (1H, m CH=CHPh), 7.10-7.30 (15H, m Arom H); δ_C(270MHz; $CDCl_3$): **99m**, 24.44 (CH_3), 54.74 (CHN), 61.92 (CHN), 126.32 (CH), 126.67 (CH), 126.88 (CH), 127.19 (CH), 127.40 (CH), 127.56 (CH), 128.40 (CH), 129.59 (CH), 130.97 (CH), 131.98 (CH), 133.15 (CH), 136.98 (C), 142.87 (C), 145.58 (C): **100m**, 24.65 (CH_3), 55.07 (CHN), 62.14 (CHN), 126.36 (CH), 126.63 (CH), 126.83 (CH), 127.13 (CH), 127.42 (CH), 127.57 (CH), 128.49 (CH), 129.50 (CH), 130.98 (CH), 131.95 (CH), 133.14 (CH), 136.93 (C), 143.33 (C), 145.63 (C); *m/z* (EI) 313.3 (M^+, 6%), 205.2(46), 105.1(100).

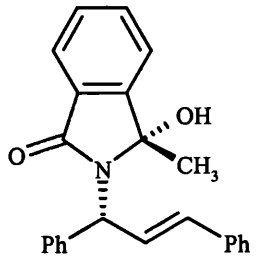


[(2*E*)-1-Ethyl-3-phenyl-2-propenyl]benzene 114.

To a flamed dried two neck flask fitted with a condenser was added alkene **92** (0.120g, 0.30mmol) and dichloroethane ($3cm^3$) under nitrogen. The solution was cooled to 0 °C and a 1M solution of diethyl zinc in hexane ($1.5cm^3$) was added followed by chloroiodomethane ($0.22cm^3$, 3.00mmol) and the reaction mixture stirred for 24 hours at room temperature. Additional amounts of diethyl zinc ($1.5cm^3$) and chloroiodomethane ($0.22cm^3$) were added and the mixture heated to reflux for 24 hours. The cooled reaction mixture was than quenched with saturated ammonium chloride ($4cm^3$) and diluted with ether ($20cm^3$). The organic fraction was separated and the aqueous back extracted with ether ($3x20cm^3$). The combined ether fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which purified by silica gel column chromatography using (light petroleum/ether 19:1) to give the *title compound* as a colourless oil (0.018g, 27%) ν_{max}/cm^{-1} 2960 (CH); δ_H(400MHz; $CDCl_3$) 0.84 (3H, t, *J* 7.3 CH_3), 1.76 (2H, m CH_2), 3.23 (1H, m C*H*CH=CH), 6.28 (2H, m CH=CH), 7.10-7.27 (10H, m Arom H); δ_C(400MHz; $CDCl_3$) 12.28 (CH_3), 28.77 (CH_2), 50.96 (CH), 126.10 (Arom CH), 126.17 (Arom CH), 126.98 (Arom CH), 127.09 (Arom CH), 127.68 (C*H*=CH), 128.44 (Arom CH), 128.66 (Arom CH), 129.21 (Arom CH), 129.42 (Arom CH), 134.21 (CH=C*H*), 137.59 (C), 144.50 (C); *m/z* (CI) 223.0 (MH^+, 47%), 207(6), 193(44), 165(65), 84(100), (EI) 222.1 (M^+, 7%), 205.1(12), 193.1(34), 84(100).



120



121

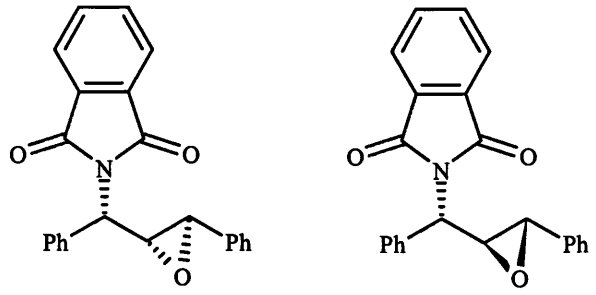
(3*R*)-2[(1*R*,2*E*)-1,3-diphenyl-2-propenyl]-3-hydroxy-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 120 and (3*S*)-2[(1*R*,2*E*)-1,3-diphenyl-2-propenyl]-3-hydroxy-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 121

To a solution of alkene **92** (0.100g, 0.295mmol) in dichloromethane ($3cm^3$) at 0 °C and under nitrogen was added diiodomethane ($0.029cm^3$, 0.354mmol) and trimethylaluminium as a 2M solution in hexane ($0.177cm^3$). The reaction mixture was stirred at room temperature for 24 hours before being diluted with dichloromethane followed by addition of NaF (0.048g, 1.15mmol in $0.5cm^3$ of H_2O) and water ($0.5cm^3$). After 30 minutes of vigorous stirring the solid was removed by filtration and the filtrate dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product as a yellow oil which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the two products as white solids.

The more mobile compound was crystallised from dichloromethane to give colourless bricks **120** (0.015g, 15%) (Found M^+, 355.1605. $C_{24}H_{21}O_2N$ requires M^+, 355.1572); (Found: C, 81.4; H, 5.95; N, 3.9. $C_{24}H_{21}O_2N$ requires C, 81.1; H, 5.95; 3.9%); ν_{max}/cm^{-1} 3290 (OH), 1675 (C=O), 1410 and 1354 (OH); δ_H(270MHz; $CDCl_3$) 1.57 (3H, s CH_3), 2.91 (1H, s OH), 3.55 (1H, d, *J* 8.6 CHN), 6.53 (1H, d, *J* 15.75 CH=C*H*Ph), 7.08 (1H, dd, *J* 8.6 and 15.75 C*H*=CHPh), 7.12-

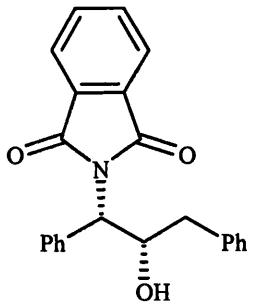
7.48 (13H, m Arom H), 7.69 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 25.59 (CH_3), 57.96 (CHN), 89.71 (N*C*(OH)CH_3), 121.91 (Arom CH), 123.94 (Arom CH), 126.62 (CH=CH), 126.93 (Arom CH), 127.32 (Arom CH), 127.56 (Arom CH), 127.77 (Arom CH), 128.06 (Arom CH), 128.33 (Arom CH), 128.76 (Arom CH), 128.89 (Arom CH), 128.98 (Arom CH), 129.23 (Arom CH), 129.92 (CH=CH), 131.00 (C), 132.39 (Arom CH), 132.12 (Arom CH), 136.85 (C), 140.51 (C), 148.16 (C), 166.28 (C); *m/z* (EI) 355.1 (M^+, 7%), 337.1(37), 264.1(28), 208.1(100).

White solid **121** (0.022g, 23%) (Found MH^+, 356.1650. $C_{24}H_{22}O_2N$ requires MH^+, 356.1650); ν_{max}/cm^{-1} 3276 (OH), 1670 (C=O); δ_H(400MHz; $CDCl_3$) 1.67 (3H, s CH_3), 2.83 (1H, s OH), 5.47 (1H, d, *J* 8.8 CHN), 6.55 (1H, d, *J* 15.6 PhC*H*=CH), 7.03 (1H, dd, *J* 8.8 and 15.6 PhCH=C*H*), 7.14-7.25 (6H, m Arom H), 7.35 (3H, m Arom H), 7.44 (4H, m Arom H), 7.61 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 25.59 (CH_3), 57.96 (CHN), 89.71 (N*C*(OH)CH_3), 121.91 (Arom CH), 123.94 (Arom CH), 126.62 (CH=CH), 126.93 (Arom CH), 127.32 (Arom CH), 127.56 (Arom CH), 127.77 (Arom CH), 128.06 (Arom CH), 128.33 (Arom CH), 128.76 (Arom CH), 128.89 (Arom CH), 128.98 (Arom CH), 129.23 (Arom CH), 129.92 (CH=CH), 131.00 (C), 132.39 (Arom CH), 132.12 (Arom CH), 136.85 (C), 140.51 (C), 148.16 (C), 166.28 (C); *m/z* (CI) 356.2 (MH^+, 100%).



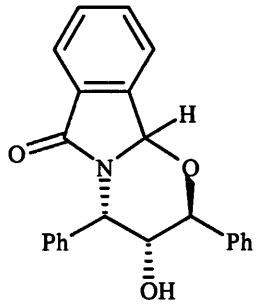
Phenyl[(1*S*)-Phthaloyl)-(2*R*,3*R*)-3-phenyloxiranyl]methane 126 and Phenyl[(1*S*)-Phthaloyl)-(2*S*,3*S*)-3-phenyloxiranyl]methane 127.

To a solution of **92** (3.00g, 8.85mmol) in dichloromethane ($100cm^3$) at 0 °C was added *m*CPBA (1.53g, 8.85mmol). The reaction mixture was stirred at room temperature for 24 hours, after which saturated aqueous sodium hydrogen carbonate ($200cm^3$) was added and stirred vigorously for 30 min. The organic fraction was separated and the aqueous back-extracted with dichloromethane ($100cm^3$ x4). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 13:7) to give compounds **126** and **127** ((diastereomeric ratio 9:1) 2.80g, 89%). Recrystallisation (ether/dichloromethane) gave epoxide **126** as colourless bricks, mp 151 °C; (Found C, 77.8; H, 4.8; N, 3.9. $C_{23}H_{17}NO_3$ requires C, 77.7; H, 4.8; N, 3.9%); $[\alpha]_D^{35}$ –1.0 (*c* 2 in $CHCl_3$), **ent-126** $[\alpha]_D^{32}$ +1.0 (*c* 2 in $CHCl_3$); ν_{max}/cm^{-1} 3061 (CH), 1770 and 1712 (NC=O); δ_H(400MHz; $CDCl_3$) 3.95 (1H, d, *J* 2.0, PhCHO), 4.23 (1H, dd, *J* 2.0 and 8.3 CHO), 5.17 (1H, d, *J* 8.3 CHN) and 7.26-7.90 (14H, m Arom H); δ_C(400MHz; $CDCl_3$) 57.31 (CHN), 59.73 (CHO), 60.59 (CHO), 123.52 (Arom CH), 125.82 (Arom CH)), 127.45 (Arom CH), 128.34 (Arom CH), 128.58 (Arom CH), 128.88 (Arom CH), 131.89 (C), 134.2 (Arom CH), 136.03 (C), 136.08 (C), 168.05 (NC=O); *m/z* (CI) 356.0 (MH^+, 43%), 236(100) and 157(88).

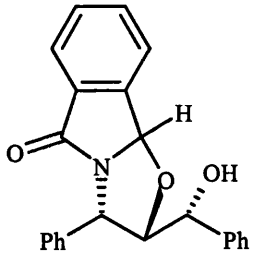


(1*S*)-Phthaloyl-(2*S*)-2-hydroxy-1,3-diphenylpropane 128.

To a solution of **126** (1.00g, 2.810mmol) in ethyl acetate (50cm^3) was added 10% Pd-C (cat.) and stirred vigorously under an atmosphere of hydrogen at room temperature for 24 hours. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo* to the crude product which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 7:3) to give the *title compound* as a colourless solid (0.985g, 98%). Recrystallisation from dichloromethane/ether gives colourless bricks, $[\alpha]_D^{31}$ –58.7 (*c* 2 in $CHCl_3$), **ent-128** $[\alpha]_D^{30}$ +61.0 (*c* 1 in $CHCl_3$); (Found MH^+, 358.1456. $C_{23}H_{19}NO_3$ requires MH^+, 358.1443); ν_{max}/cm^{-1} 3460 (OH), 3061, 3029 and 2923 (CH), 1769 and 1707 (NC=O); δ_H(400MHz; $CDCl_3$) 1.63 (1H, s OH), 2.64 (1H, dd, *J* 8.8 and 13.7 CH_2), 2.81 (1H, dd, *J* 3.5 and 13.7 CH_2), 5.08 (1H, dt, *J* 3.5 and 8.8 CHO), 5.28 (1H, d, *J* 8.8 CHN), 7.16-7.40 (8H, m Arom H), 7.60 (2H, m Arom H), 7.69 (2H, m Arom H), 7.81 (2H, m Arom H); δ_C(270MHz; $CDCl_3$) 41.38 (CH_2), 60.71 (CHN), 71.17 (CHO), 123.30 (Arom CH), 126.59 (Arom CH), 128.28 (Arom CH), 128.50 (Arom CH), 128.83 (Arom CH), 128.86 (Arom CH), 129.36 (Arom CH), 131.78 (C), 134.01 (Arom CH), 137.49 (C), 137.76 (C), 168.85 (NC=O); *m/z* (FAB+) 358.2 (MH^+, 100%).



129

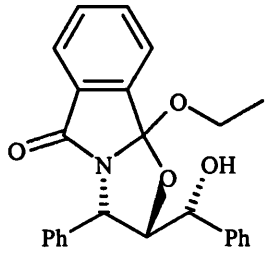


130

(2*S*,3*R*,4*S*)-3-Hydroxy-2,4-diphenyl-3,4-dihydro-2*H*-[1,3]oxazino[2,3*a*] isoindol-6-(10b*H*)-one 129 and **(2*R*,3*S*)-2-[(*S*)-hydroxy(phenyl)methyl]-3-phenyl-2,3-dihydro[1,3*a*]isoindol-5-(9b*H*)-one 130.**

To a solution of **126** (0.200g, 0.563mmol) in THF (4cm^3) was added $NaBH_3CN$ (0.426g, 6.756mmol) followed by $BF_3.Et_2O$ (0.421cm^3, 3.378mmol) and stirred at room temperature for 1 hours. The reaction mixture was quenched with brine (10cm^3), diluted with ethyl acetate (5cm^3) and vigorously stirred for 20 minutes. The organic layer was separated and the aqueous back-extracted with ethyl acetate (15cm^{3}x6). The combined ethyl acetate fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 6:4) to give **129** as a white foam (0.074g, 37%) (Found: C, 77.0; H, 5.4; N, 4.0. $C_{23}H_{19}NO_3$ requires C, 77.3; H, 5.4; N, 4.0%); (Found MH^+, 358.1457. $C_{23}H_{19}NO_3$ requires MH^+, 358.1443); ν_{max}/cm^{-1} 3427 (OH), 1700 (C=O); δ_H(400MHz; $CDCl_3$) 4.12 (1H, dd, *J* 6.2 and 8.9 CHO), 5.05 (1H, d, *J* 8.9 CHO), 5.88 (1H, d, *J* 6.2 CHN), 6.23 (1H, s NCHO), 7.21-7.39 (8H, m Arom H), 7.60 (5H, m Arom H), 7.88 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 54.30 (CHN), 71.78 (CHO), 79.91 (CHO), 83.68 (NCHO), 124.20 (Arom CH), 124.34 (Arom CH), 127.81 (Arom CH), 128.20 (Arom CH), 129.11 (Arom CH), 129.25 (Arom CH), 130.59 (Arom CH), 132.56 (C), 132.76 (Arom CH), 136.80 (C), 137.86 (C), 141.61 (C), 167.47 (NC=O); *m/z*

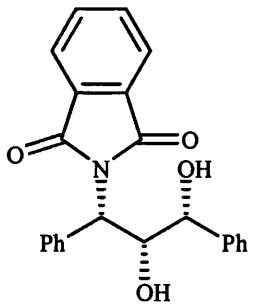
(CI) 358.1 (MH^+, 100%) and **130** as a white foam (0.106g, 53%) $[\alpha]_D^{33}$ -78.9 (*c* 1.8 in $CHCl_3$); (Found MH^+, 358.1458. $C_{23}H_{19}NO_3$ requires MH^+, 358.1443); ν_{max}/cm^{-1} 3264 (OH), 3029 and 2924 (CH), 1699 and 1686 (C=O); δ_H(400MHz; $CDCl_3$) 2.00 (1H, s OH), 4.59 (1H, d, *J* 9.4 CHO), 4.68 (1H, dd, *J* 5.3 and 9.3 CHO), 5.33 (1H, d, *J* 5.3 CHN), 6.31 (1H, s NCHO), 7.25-7.79 (14H, m Arom H); δ_C(400MHz; $CDCl_3$) 59.24 (CHN), 69.75 (CHO), 77.30 (CHO), 81.36 (NCHO), 123.83 (Arom CH), 124.32 (Arom CH), 126.93 (Arom CH), 128.80 (Arom CH), 129.10 (Arom CH), 129.18 (Arom CH), 130.66 (Arom CH), 132.65 (Arom CH), 133.48 (C), 134.71 (C), 140.03 (C), 141.96 (C), 168.99 (NC=O); *m/z* (CI) 358.1 (MH^+, 100%).



(2*S*,3*S*)-9b-Ethoxy-2-[(*R*)-hydroxy(phenyl)methyl]-3-phenyl-2,3-dihydro[1,3]oxazolo[2,3-*a*]isoindol-5(9b*H*)-one 134

To the epoxide **126** (0.106g, 0.300mmol) in dry ethanol (2.5 cm^3) was added ethanethiol (44µl, 0.60mmol) and the reaction mixture stirred at room temperature for 24 hours with a further 72 hours heated at reflux temperature. The cooled reaction mixture was diluted with dichloromethane (15cm^3) and water (15cm^3) and separated. The aqueous fraction was back-extracted with dichloromethane (15cm^3x4) and the combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the acetal **134** as

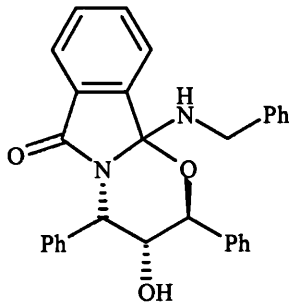
a colourless oil (0.046g, 38%) ν_{max}/cm^{-1} 3262 (OH), 2934 (CH), 1724 and 1649 (NC=O); δ_H(400MHz; $CDCl_3$) 1.23 (3H, m CH_3CH_2), 1.90 (1H, d, *J* 3.4 OH), 3.98 (1H, m CH_2CH_3), 4.11 (1H, m CH_2CH_3), 4.50 (1H, dd, *J* 3.4 and 8.8 CHOH), 4.90 (1H, dd, *J* 8.8 and 9.8 CHO), 5.57 (1H, d, *J* 9.8 CHN), 7.26 (4H, m Arom H), 7.40 (4H, m Arom H), 7.50 (2H, m Arom H), 7.67 (1H, m Arom H), 7.82 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 14.12 (CH_3), 61.45 (CH_2), 71.76 (CHN), 72.00 (CHOH), 85.95 (CHO), 126.77 (Arom CH), 127.34 (C), 127.87 (Arom CH), 128.13 (Arom CH), 128.16 (Arom CH), 128.35 (Arom CH), 128.49 (Arom CH), 128.75 (Arom CH), 128.86 (Arom CH), 130.21 (Arom CH), 130.81 (Arom CH), 132.84 (C), 137.05 (C), 140.80 (C), 164.79 (NC(O)OEt), 167.57 (NC=O); *m/z* (FAB+) 402.1 (MH^+, 100%).



(1*S*,2*R*,3*R*)-*N*-Phthaloyl-2,3-dihydroxy-1,3-diphenylpropane 136.

The epoxide **126** (0.200g, 0.536mmol) in anhydrous ethanol ($7cm^3$) was heated to reflux for 7 days allowed to cool and concentrated *in vacuo* to a straw coloured oil. The crude product was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a cream solid (0.191g, 91%) (Found MH^+, 374.1389. $C_{23}H_{19}O_4N$ requires MH^+, 374.1392); ν_{max}/cm^{-1} 3450 (OH), 3062, 3032 and 2923 (CH), 1768 and 1703 (NC=O); δ_H(270MHz; $CDCl_3$) 2.58 (1H, s OH), 3.88 (1H, m OH), 4.60 (1H, d, *J* 5.4 CHOH), 5.01 (1H, m CHOH), 5.38 (1H, d, *J* 6.8 CHN), 7.25-7.33 (8H, m Arom H), 7.45 (2H, m

Arom H), 7.68 (2H, m Arom H), 7.78 (2H, m Arom H); δ_C(270MHz; $CDCl_3$) 56.45 (CHN), 74.23 (CHO), 74.41 (CHO), 123.18 (Arom CH), 127.01 (Arom CH), 128.21 (Arom CH), 128.38 (Arom CH), 128.62 (Arom CH), 131.69 (C), 134.19 (Arom CH), 136.74 (C), 139.57 (C), 169.11 (NC=O); *m/z* (EI) 373.1 (M^+, 100%).

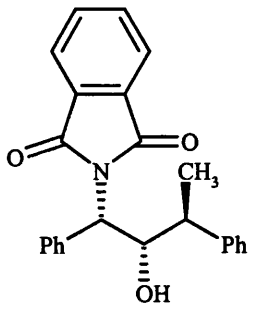


134

(2*S*,3*R*,4*S*)-10b-(benzylamino)-3-hydroxy-2,4-diphenyl-3,4-dihydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one 137.

To a solution of **126** (0.200g, 0.563mmol) in THF (7.5cm^3) was added benzylamine (0.134cm^3, 1.29mmol) at 0 °C and stirred for 5 days at room temperature. The reaction mixture was diluted with dichloromethane (10cm^3) and water (20cm^3), the organic fraction separated and the aqueous back-extracted with dichloromethane (10cm^3x5). The combined dichloromethane fractions were washed with saturated brine (30cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 7:3) to give the *title compound* as a flaky white solid (0.205g, 79%) $[\alpha]_D^{34}$ +83.0 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 3421 (NH), 3054 and 2987 (CH), 1661 (NC=O); δ_H(400MHz; $CDCl_3$) 1.74 (1H, s OH), 3.37 (1H, t, *J* 2.4 CHOH), 4.01 (1H, d, *J* 2.4 CHO), 4.43 (1H, dd, *J* 5.4 and 14.65 CH_2), 4.54 (1H, dd, *J* 5.4 and 14.65 CH_2), 5.55 (1H, dd, *J* 2.4 and 8.8 CHN), 6.83

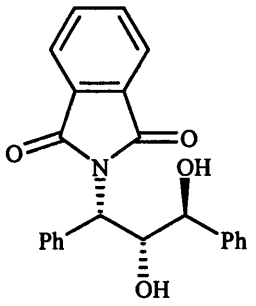
(1H t, *J* 5.4 NH), 7.25-7.57 (14H, m Arom H); δ_C(400MHz; $CDCl_3$) 44.12 (CH_2), 52.56 (CHN), 55.90 (CHO), 63.86 (CHOH), 127.26 (Arom CH), 127.55 (Arom CH), 127.76 (Arom CH), 127.85 (Arom CH), 128.05 (Arom CH), 128.12 (Arom CH), 128.32 (Arom CH), 128.45 (Arom CH), 128.54 (Arom CH), 128.72 (Arom CH), 129.00 (Arom CH), 130.32 (Arom CH), 130.48 (Arom CH), 134.38 (C), 134.87 (C), 136.31 (C), 137.67 (C), 139.17 (C), 168.41 (NC(NH)O), 168.92 (NC=O); *m/z* (FAB) 463.1 (MH^+, 100%).



(1*S*,2*S*,3*S*)-*N*-Phthaloyl-2-hydroxy-1,3-diphenylbutane 138.

To CuBr.SMe_2 (0.348g, 1.689mmol) in THF (4cm^3) at –78 °C was added MeMgBr (1.126cm^3, 3M solution in diethyl ether) drop wise and allowed to warm to 0 °C. Epoxide **123** (0.200g, 0.563mmol) in THF (2cm^3) was added to the cuprate drop wise over 5 minutes and the mixture was stirred at –10 °C for 3 hours before being quenched with saturated ammonium chloride (35cm^3) then vigorously stirred at room temperature for 90 minutes. The reaction mixture was diluted with dichloromethane (15cm^3) and organic fraction separated. The aqueous back-extracted with dichloromethane (15cm^3x4) and the combined dichloromethane fractions were washed with saturated brine (50cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a cream foam (0.105g, 50%) (Found: C, 77.3; H, 6.0; N, 3.6.

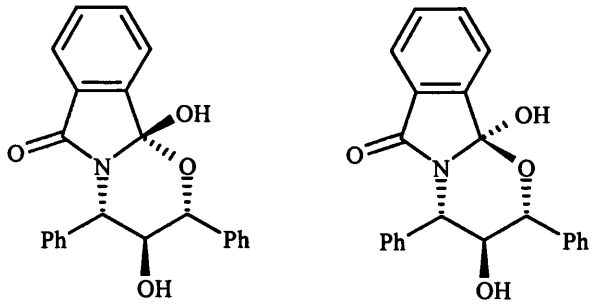
$C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%); **138** $[\alpha]_D^{27}$ +2.0 (*c* 1.5 in $CHCl_3$), **ent-138** $[\alpha]_D^{32}$ -2.0 (*c* 2 in $CHCl_3$); (Found: M^+, 372.1603. $C_{24}H_{22}NO_3$ requires M^+, 372.1599); ν_{max}/cm^{-1} 3458 (OH), 2928 (CH), 1768 and 1703 (NC=O); δ_H(400MHz; $CDCl_3$) 1.39 (3H, d, *J* 7.3 CH_3), 2.74 (1H, d, *J* 8.3 OH), 2.80 (1H, qd, *J* 3.4 and 7.3 $CHCH_3$), 4.98 (1H, dd, *J* 3.4 and 8.5 CHOH), 5.12 (1H, d, *J* 8.5 CHN), 7.15-7.45 (8H, m Arom H), 7.52 (2H, d, *J* 6.8 Arom H), 7.64 (2H, dd, *J* 2.9 and 5.4 Arom H), 7.74 (2H, dd, *J* 2.9 and 5.4 Arom H); δ_C(400MHz; $CDCl_3$) 19.86 (CH_3), 42.28 ($CHCH_3$), 59.22 (CHN), 74.00 (CHO), 123.23 (Arom CH), 126.76 (Arom CH), 128.18 (Arom CH), 128.31 (Arom CH), 128.75 (Arom CH), 128.97 (Arom CH), 131.71 (C), 133.96 (Arom CH), 137.48 (C), 141.42 (C), 168.95 (NC=O); *m/z* (CI) 372.1 (MH^+, 100%).



(1*S*,2*R*,3*S*)-*N*-Phthaloyl-2,3-dihydroxy-1,3-diphenylpropane 139.

To a solution of epoxide **126** (1.20g, 3.380mmol) in THF ($20cm^3$) was added 1M sulfuric acid ($3.4cm^3$). The reaction mixture was stirred at room temperature for 48 hours before being diluted with dichloromethane ($50cm^3$) and saturated aqueous sodium hydrogen carbonate ($40cm^3$) then vigorously stirred for 30 minutes. The organic fraction was separated and the aqueous back-extracted with dichloromethane ($40x3cm^3$). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica

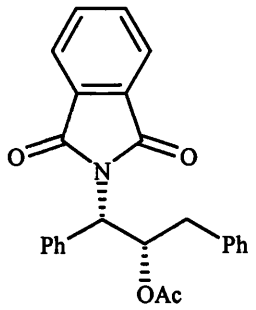
gel column chromatography using (light petroleum/ethyl acetate 6:4) to yield the *title compound* as a white foam (1.210g, 96%) **139** $[\alpha]_D^{33}$ –8.5 (*c* 2 in $CHCl_3$), **ent-139** $[\alpha]_D^{33}$ +7.5 (*c* 2 in $CHCl_3$); (Found MH^+, 374.1390. $C_{23}H_{19}NO_4$ requires MH^+, 374.1392); ν_{max}/cm^{-1} 3441 (OH), 1767 and 1705 (NC=O), 1390 (OH); δ_H(270MHz; $CDCl_3$) 2.56 (1H, m OH), 3.84 (1H, m OH), 4.56 (1H, d, *J* 5.5 CHOH), 4.97 (1H, dd, *J* 5.5 and 7.1 CHOH), 5.33 (1H, d, *J* 7.1 CHN), 7.27-7.43 (10H, m Arom H), 7.65 (2H, dd, *J* 2.9 and 5.4 Arom H), 7.75 (2H, dd, *J* 2.9 and 5.4 Arom H); δ_C(400MHz; $CDCl_3$) 56.63 (CHN), 74.33 (CHOH), 75.19 (CHOH), 123.49 (Arom CH), 127.35 (Arom CH), 128.24 (Arom CH), 128.39 (Arom CH), 128.55 (Arom CH), 128.72 (Arom CH), 131.71 (C), 134.19 (C), 136.75 (C), 139.62 (C), 168.07 (NC=O); *m/z* (CI) 374.3 (MH^+, 26%), 356(71) and 236(100).



(2*R*,3*S*,4*S*,10b*R*)-3,10b-dihydroxy-2,4-diphenyl-3,4-dihydro-2*H*[1,3]oxazino [2,3-*a*]isoindol-6(10b*H*)-one 141 and **(2*R*,3*S*,4*S*,10b*S*)-3,10b-dihydroxy-2,4-diphenyl-3,4-dihydro-2*H*[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one 142.**

To epoxide **127** (1.20g, 3.380mmol) in THF ($25cm^3$) was added 1M sulfuric acid ($3.4cm^3$). The reaction mixture was stirred at room temperature for 48 hours before being diluted with dichloromethane ($50cm^3$) and saturated aqueous sodium hydrogen carbonate ($40cm^3$) then vigorously stirred for 30 minutes. The organic fraction was separated and the aqueous back-extracted with dichloromethane

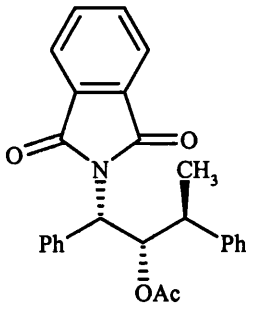
($40x3cm^3$). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 6:4) to yield a white foam containing the hemiacetals **141** and **142** (1.210g, 96%) ν_{max}/cm^{-1} 3451 (OH), 1768 and 1705 (NC=O); δ_H(400MHz; $CDCl_3$) [the two individual structures, **141** and **142**, could not be resolved so the two sets of signals identified in the ^1H NMR have just be assigned as H_a and H_b] 1.75 (1H, s OH), 2.60 (1H, s OH), 3.02 (1H, s OH), 3.49 (1H, s OH), 4.76 (1H, d, *J* 4.9 CH_aOH), 4.88 (1H, d, *J* 5.4 CH_bOH), 5.15 (1H, dd, *J* 5.4 and 6.8 CH_bOH), 5.21 (1H, dd, *J* 4.9 and 8.3 CH_aOH), 5.49 (1H, d, *J* 8.3 CH_aN), 5.77 (1H, d, *J* 6.8 CH_bN), 7.09-7.91 (14H, m Arom H); δ_C(400MHz; $CDCl_3$) 55.80 (CHN), 56.66 (CHN), 72.97 (CHO), 73.17 (CHO), 74.09 (CHO), 74.16 (CHO), 123.17 (Arom CH), 123.47 (Arom CH), 126.03 (Arom CH), 126.28 (Arom CH), 126.59 (Arom CH), 127.34 (Arom CH), 128.35 (Arom CH), 128.49 (Arom CH), 128.64 (Arom CH), 128.95 (Arom CH), 131.57 (C), 133.91 (Arom CH), 134.07 (Arom CH), 134.13 (Arom CH), 134.16 (Arom CH), 136.78 (C), 136.96 (C), 140.16 (C), 168.23 (NC(O)OH), 168.45 (NC=O); *m/z* (CI) 374.0 (MH^+, 34%), 356(100).



(1*S*,2*S*)-1-Benzyl-2-phthaloyl-2-phenylethylacetate 154.

To a solution of **128** (1.00g, 2.801mmol) in dichloromethane ($15cm^3$) was added Et_3N ($0.434cm^3$, 3.361mmol) and 4-(dimethylamino)pyridine (0.010g) and cooled

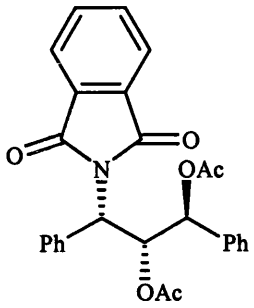
to 0 °C. Ac_2O (0.528cm^3, 5.602mmol) was added and the mixture stirred at room temperature for 2 hours before being diluted with dichloromethane (15cm^3) and saturated sodium hydrogen carbonate (30cm^3) and vigorously stirred for 30 minutes. The dichloromethane fraction was separated and the aqueous back-extracted with dichloromethane (20cm^{3}x4). The combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 7:3) to yield the *title compound* as a white foam (1.110g, 100%) (Found: C, 75.0; H, 5.5; N, 3.7. $C_{25}H_{21}NO_4$ requires C, 75.2; H, 5.3; N, 3.5%); **154** $[\alpha]_D^{32}$ +64.0 (*c* 1 in $CHCl_3$), **ent-154** $[\alpha]_D^{30}$ –58.5 (*c* 2 in $CHCl_3$); (Found M^+ 399.1476. $C_{25}H_{21}NO_4$ requires M^+, 399.1470); ν_{max}/cm^{-1} 1744 and 1715 (C=O); δ_H(400MHz; $CDCl_3$) 1.79 (3H, s CH_3), 2.69 (1H, dd, *J* 7.3 and 14.6 CH_2), 3.05 (1H, dd, *J* 3.9 and 14.6 CH_2), 5.37 (1H, d, *J* 10.7 CHN), 6.52 (1H, ddd, *J* 3.9, 7.3 and 10.7 CHO), 7.07 (2H, m Arom H), 7.22 (3H, m Arom H), 7.34 (3H, m Arom H), 7.72 (4H, m Arom H), 7.78 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 21.86 (CH_3), 39.27 (CH_2), 58.78 (CHN), 72.73 (CHO), 124.40 (Arom CH), 127.75 (Arom CH), 129.30 (Arom CH), 129.79 (Arom CH), 129.94 (Arom CH), 130.71 (Arom CH), 130.96 (Arom CH), 132.65 (C), 135.06 (Arom CH), 136.87 (C), 137.20 (C), 168.89 (NC=O), 170.74 ($C(O)CH_3$); *m/z* (CI) 400.2 (MH^+, 100%).



(1*S*,2*S*)-1-[(*S*)-(phthaloyl)(phenyl)methyl]-2-phenylpropyl acetate 155.

To alcohol **138** (0.350g, 0.943mmol) in dichloromethane (10cm^3) was added Et_3N (0.135cm^3, 1.037mmol) and 4-(dimethylamino)pyridine (0.005g) and cooled to 0 °C. Ac_2O (0.195cm^3, 2.074mmol) was added and the mixture stirred at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane (20cm^3) and saturated sodium hydrogen carbonate (20cm^3) and stirred vigorously for 30 minutes. The organic layer was separated and the aqueous back-extracted with dichloromethane (20cm^{3}x3). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a white foam (0.305g, 79%) (Found C, 75.2; H, 5.8; N, 3.3. $C_{26}H_{23}NO_4$ requires C, 75.5; H, 5.6; N, 3.4%); (Found: MH^+, 414.1714. $C_{26}H_{23}NO_4$ requires MH^+, 414.1705); ν_{max}/cm^{-1} 3030, 2971 and 2933 (CH), 1774 and 1746 (NC=O) and 1715 (C=O); δ_H(400MHz; $CDCl_3$) 1.30 (3H, d, *J* 7.3 $CHCH_3$), 1.96 (3H, s $COCH_3$), 3.00 (1H, dq, *J* 7.3 and 2.75 $CHCH_3$), 5.08 (1H, d, *J* 11.0 CHN), 6.60 (1H, dd, *J* 2.75 and 11.0 CHO), 6.96 (2H, m Arom H), 7.24 (3H, m Arom H), 7.31 (3H, m Arom H), 7.49 (2H, m Arom H), 7.64 (2H, dd, *J* 2.9 and 5.4 Arom H), 7.76 (2H, dd, *J* 2.9 and 5.4 Arom H); δ_C(400MHz; $CDCl_3$) 19.56 (CH_3), 20.83 (CH_3), 41.18 (CH), 56.82 (CHN), 74.19 (CHO), 123.27 (Arom CH), 126.97 (Arom CH), 128.14 (Arom CH), 128.52 (Arom CH), 128.60 (Arom

CH), 128.93 (Arom CH), 130.41 (Arom CH), 131.54 (C), 133.94 (Arom CH), 135.31 (C), 140.59 (C), 167.73 (NC=O), 170.15 ($OC(O)CH_3$); *m/z* (FAB+) 414.3 (M^+, 100%).



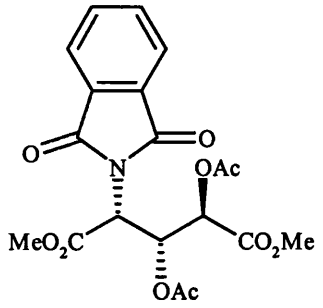
(1*S*,2*R*,3*S*)-2-(Acetoxy)-3-(phthaloyl)-1,3-diphenylpropyl acetate 156.

To diol **139** (1.150g, 3.08mmol) in dichloromethane ($15cm^3$) was added Et_3N ($0.79cm^3$, 6.16mmol) and 4-(dimethylamino)pyridine (0.010g) and cooled to 0 °C. Ac_2O ($1.16cm^3$, 12.32mmol) was added and stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane ($20cm^3$) and saturated aqueous hydrogen carbonate ($50cm^3$) and stirred vigorously for 30 minutes. The organic fraction was separated and the aqueous back-extracted with dichloromethane ($20cm^3$x3). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 7:3) to yield *the title compound* as a white foam (1.405g, 98%) **156** $[\alpha]_D^{29}$ +73 (*c* 2 in $CHCl_3$), **ent-156** $[\alpha]_D^{30}$ -76.0 (*c* 1 in $CHCl_3$); (Found MH^+, 458.1593. $C_{27}H_{23}NO_6$ requires MH^+, 458.1602); ν_{max}/cm^{-1} 3033 (CH), 1750 and 1716 (NC=O); δ_H (400MHz; $CDCl_3$) 1.91 (3H, s CH_3), 2.01 (3H, s CH_3), 5.25 (1H, d, *J* 11.0 CHN), 5.93 (1H, d, *J* 3.7 CHO), 6.81 (1H, dd, *J* 3.7 and 11.0 CHO), 7.12 (2H, m Arom H), 7.25-7.32 (6H, m Arom H), 7.60 (2H, m Arom H), 7.65 (2H, dd, *J* 3.05 and 5.5 Arom H), 7.76

(2H, dd, *J* 3.05 and 5.5 Arom H); δ_C(400MHz; $CDCl_3$) 20.69 (CH_3), 20.82 (CH_3), 55.09 (CNH), 71.22 (CHO), 74.35 (CHO), 123.34 (Arom CH), 127.99 (Arom CH), 128.11 (Arom CH), 128.57 (Arom CH), 128.75 (Arom CH), 128.81 (Arom CH), 129.96 (Arom CH), 131.42 (C), 134.02 (Arom CH), 134.55 (C), 134.73 (C), 167.53 (NC=O), 169.52 ($OC(O)CH_3$), 169.67 ($OC(O)CH_3$); *m/z* (CI) 475.2 (MNH_4^+, 100%).

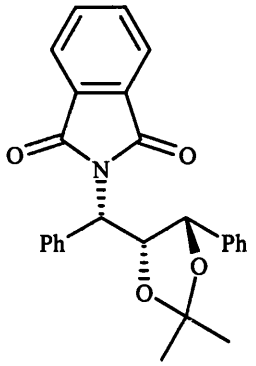
General procedure (3) for the oxidation of phenyl compounds to dimethyl esters.

To a solution of the diphenyl substrate (1 mmol) in ethyl acetate ($10cm^3$), acetonitrile ($10cm^3$) and water ($14cm^3$) was added $NaIO_4$ (28 mmol) and stirred at room temperature for 10 minutes. $RuCl_3.H_2O$ (0.017mmol) was added and vigorously stirred at 30 °C for 48 hours. Diluted with ethyl acetate ($50cm^3$) and water ($100cm^3$) and separated. The aqueous back-extracted with ethyl acetate ($50cm^3$x6) and the combined organic fractions diluted with diethyl ether ($100cm^3$) and stirred for 30 minutes to precipitate the RuO_2. The organic fraction is then dried ($MgSO_4$), filtered through a pad of Celite and concentrated *in vacuo* to give the crude diacid which was taken directly, diluted with ethanol ($10cm^3$) and treated with diazomethane (generated from diazald® (5 mmol) and KOH (5 mmol) in ethanol ($10cm^3$)) bubbled through with a stream of nitrogen. The crude methyl ester was then concentrated *in vacuo* and purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2).



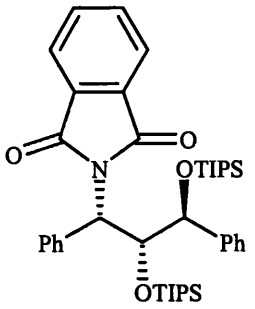
1,5-Dimethyl-2,3-di-*O*-acetyl-4-deoxy-4-phthaloyl-*D*-xylarate 162.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum-ethyl acetate 8:2) to give the *title compound* **162** as a cream foam (0.117g, 32%) $[\alpha]_D^{32}$ +20.7 (*c* 1.5 in $CHCl_3$), **ent-162** $[\alpha]_D^{32}$ –17.5 (*c* 1 in $CHCl_3$); (Found FAB^+ 422.1091. $C_{19}H_{19}NO_{10}$ requires MH^+, 422.1087); ν_{max}/cm^{-1} 1755 and 1750 (C=O), 1723 (NC=O); δ_H(400MHz; $CDCl_3$) 1.85 (3H, s $OCCH_3$), 2.09 (3H, s $OCCH_3$), 3.69 (3H, s OCH_3), 3.73 (3H, s OCH_3), 5.32 (1H, d, *J* 4.9 CHN), 5.36 (1H, d, *J* 6.35 CHO), 6.03 (1H, dd, *J* 4.9 and 6.35 CHO), 7.71 (2H, dd, *J* 2.9 and 5.4 Arom H), 7.81 (2H, dd, *J* 2.9 and 5.4 Arom H); δ_C(400MHz; $CDCl_3$) 20.39 (CH_3), 50.37 (CHN), 53.11 (CH_3), 68.89 (CHO), 70.78 (CHO), 123.76 (Arom CH), 131.44 (C), 134.47 (Arom CH), 166.83 (CO_2Me), 167.17 (NC=O), 169.04 ($OC(O)CH_3$), 169.51 ($OC(O)CH_3$); *m/z* (CI) 422.1 (MH^+, 100%).



(1*S*,2*R*,3*S*)-3-Phthaloyl-2-(2,2-dimethyl-1,3-dioxolane)-1,3-diphenylpropane 165.

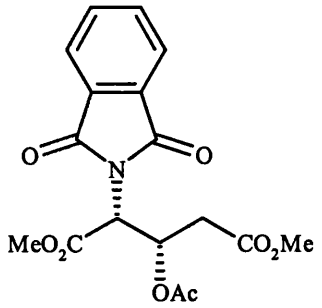
To a solution of 1N-(phthaloyl)-2,3-hydroxy-1,3-diphenylpropane **139** (0.140g, 0.375mmol) in dry acetone ($2cm^3$) was added pTSA (0.035g, 0.187mmol) and some 4Å molecular sieves. The mixture was stirred for 16 hours at room temperature before being transferred into saturated sodium hydrogen carbonate ($25cm^3$) and vigorously stirred for 30 minutes. The mixture was extracted with ether ($25cm^3$x4) and the combined organic fractions dried ($MgSO_4$) and concentrated *in vacuo* to the crude product which was purified by silica gel column chromatography using (light petroleum/ether 2:8) to give the *title compound* as a white foam (0.133g, 86%) ν_{max}/cm^{-1} 3034, 2987 and 2938 (CH), 1770 and 1712 (NC=O); δ_H(400MHz; $CDCl_3$) 1.41 (3H, s CH_3), 1.46 (3H, s CH_3), 4.98 (1H, d, *J* 11.0 CHN), 5.22 (1H, d, *J* 6.1 CHO), 5.83 (1H, dd, *J* 6.1 and 11.0 CHO), 6.90-7.04 (10H, m Arom H), 7.58 (2H, dd, *J* 3.0 and 5.5 Arom H), 7.70 (2H, dd, *J* 3.0 and 5.5 Arom H); δ_C(400MHz; $CDCl_3$) 25.19 (CH_3), 27.33 (CH_3), 55.38 (CHN), 75.68 (CHO), 79.17 (CHO), 108.75 (C), 123.17 (Arom CH), 127.22 (Arom CH), 127.53 (Arom CH), 127.75 (Arom CH), 127.82 (Arom CH), 128.09 (Arom CH), 129.14 (Arom CH), 131. 92 (C), 133.76 (Arom CH), 135.74 (C), 136.01 (C), 168.56 (C); *m/z* (CI) 414.1 (M^+, 37%), 398.2(42), 356.1(100).



(1*S*,2*R*,3*S*)-Phthaloyl-1,3-diphenyl-2,3-bis[(triisopropylsilyl)oxy]propane 167.

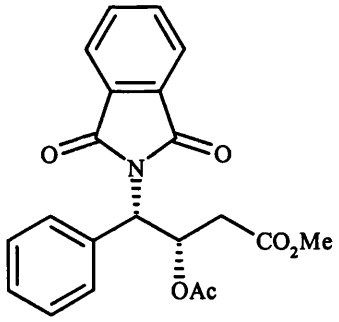
To diol **139** (0.240g, 0.643mmol) in anhydrous dichloromethane (5cm^3) under an atmosphere of nitrogen was added 2,5-lutidine (0.371cm^3, 3.22 mmol) and the mixture cooled to 0 °C. Triisopropylsilyl triflate (0.518cm^3, 1.93mmol) was added to the mixture at 0 °C and then stirred at room temperature for 30 minutes before being diluted with dichloromethane (20cm^3) and water (75cm^3). The dichloromethane was separated and the aqueous back-extracted with dichloromethane (3x20cm^3). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as yellow oil which was purified by silica gel column chromatography using (light petroleum/ether 9:1) to give the *title compound* as a white foam (0.240g, 54%) (Found MH^+, 686.4054. $C_{41}H_{59}O_4NSi_2$ requires MH^+, 686.4060); ν_{max}/cm^{-1} 2943 and 2866 (CH), 1770 and 1714 (NC=O); δ_H(400MHz; $CDCl_3$) 0.82-1.09 (42H, m 12xCH_3 and 6xC*H*$(CH_3)_2$), 4.90 (1H, d, *J* 1.2 CHO), 5.20 (1H, m CHO), 5.72 (1H, d, *J* 10.7 CHN), 7.09 (2H, m Arom H), 7.17 (3H, m Arom H), 7.24 (3H, m Arom H), 7.52 (2H, m Arom H), 7.62 (2H, m Arom H), 7.72 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 12.53 (CH), 17.79 (CH_3), 18.16 (CH_3), 18.40 (CH_3), 18.69 (CH_3), 19.00 (CH_3), 58.13 (CHN), 76.37 (CHO), 77.81 (CHO), 122.82 (Arom CH), 127.14 (Arom CH), 127.30 (Arom CH), 127.83 (Arom CH), 128.71 (Arom CH), 130.50

(Arom CH), 132.86 (Arom CH), 133.76 (Arom CH), 137.09 (C), 140.10 (C), 168.34 (NC=O); *m/z* (FAB) 685.3 (M^+, 100%)



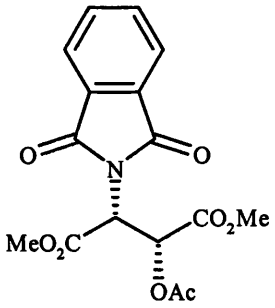
1,5-Dimethyl-3-*O*-acetyl-2,4-dideoxy-2-phthaloyl-*D*-threo pentarate 168.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a straw coloured oil (0.048g, 15%) **168** $[\alpha]_D^{31}$ +36.0 (*c* 1 in $CHCl_3$), **ent-168** $[\alpha]_D^{33}$ –41.0 (*c* 1 in $CHCl_3$); (Found MH^+, 364.1032. $C_{17}H_{17}NO_8$ requires MH^+, 364.1032); ν_{max}/cm^{-1} 2952 and 2925 (CH), 1746 and 1720 (NC=O); δ_H(400MHz; $CDCl_3$) 1.93 (3H, s CH_3), 2.84 (1H, dd, *J* 6.8 and 16.6 CH_2), 2.91 (1H, dd, *J* 5.9 and 16.6 CH_2), 3.72 (3H, s CH_3), 3.75 (3H, s CH_3), 5.24 (1H, d, *J* 5.9 CHN), 5.99 (1H, m CHO), 7.77 (2H, dd, *J* 2.9 and 5.4 Arom H), 7.89 (2H, dd, *J* 2.9 and 5.4 Arom H); δ_C(400MHz; $CDCl_3$) 20.70 (CH_3), 36.55 (CH_2), 52.02 (CH_3), 52.96 (CH_3), 52.96 (CHN), 67.57 (CHO), 123.77 (Arom CH), 131.56 (C), 134.43 (Arom CH), 166.98 (CO_2Me), 167.09 (CO_2Me), 169.51 (NC=O), 170.09 ($OC(O)CH_3$); *m/z* (FAB+) 364.1 (MH^+, 100%).



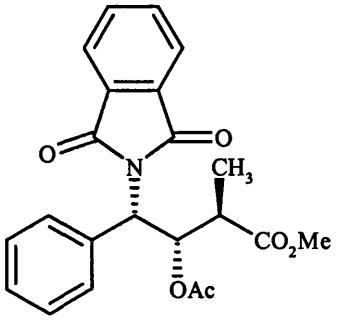
Methyl-(3*S*,4*S*)-3-(acetyloxy)-4-phthaloyl-4-phenylbutanoate 169.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a cream foam (0.037g, 11%) **169** $[\alpha]_D^{31}$ +22.0 (*c* 1 in $CHCl_3$), **ent-169** $[\alpha]_D^{33}$ –17.0 (*c* 1 in $CHCl_3$); (Found M^+, 381.1219. $C_{21}H_{19}NO_6$ requires M^+, 381.1212); ν_{max}/cm^{-1} 2952 (CH), 1774 and 1715 (NC=O), 1747 (C=O); δ_H(400MHz; $CDCl_3$) 1.91 (3H, s CH_3), 2.46 (1H, dd, *J* 6.7 and 15.6 CH_2), 2.71 (1H, dd, *J* 4.0 and 15.6 CH_2), 3.63 (3H, s OCH_3), 5.60 (1H, d, *J* 10.7 CHN), 6.54 (1H, ddd, *J* 4.0, 6.7 and 10.7 CHO), 7.36 (3H, m Arom H), 7.68 (4H, m Arom H), 7.81 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 20.72 (CH_3), 37.05 (CH_2), 51.85 (CH_3), 57.48 (CHN), 68.51 (CHO), 123.36 (Arom CH), 127.21 (Arom CH), 128.93 (Arom CH), 129.63 (Arom CH), 131.48 (C), 134.05 (Arom CH), 135.41 (C), 167.81 (NC=O), 169.73 (CO_2Me), 169.92 ($OC(O)CH_3$); *m/z* (CI) 382 (MH^+, 78%), 322(100), 290(49), 186(48) and 148(49).



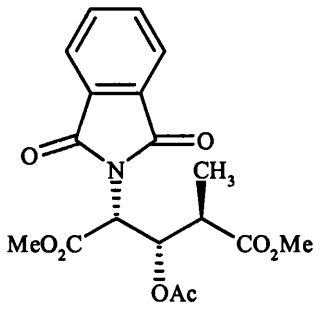
Dimethyl-(2*R*,3*R*)-2-(acetyloxy)-3-phthaloyl-butanoate 170.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a colourless oil (0.015g, 5%) **170** $[\alpha]_D^{31}$ +37.0 (*c* 1 in $CHCl_3$), **ent-170** $[\alpha]_D^{34}$ –35.0 (*c* 1 in $CHCl_3$); (Found MH^+, 350.0884. $C_{16}H_{15}NO_8$ requires MH^+, 350.0875); ν_{max}/cm^{-1} 2957 (CH), 1751 (NC=O), 1724 (C=O); δ_H(400MHz; $CDCl_3$) 1.98 (3H, s CCH_3), 3.71 (3H, s OCH_3), 3.73 (3H, s OCH_3), 5.34 (1H, d, *J* 4.4 CHN), 5.84 (1H, d, *J* 4.4 CHO), 7.70 (2H, dd, *J* 3.1 and 5.5 Arom H), 7.81 (2H, dd, *J* 3.1 and 5.5 Arom H); δ_C(400MHz; $CDCl_3$) 20.36 (CH_3), 51.79 (CHN), 52.95 (CH_3), 53.24 (CH_3), 69.48 (CHO), 123.79 (Arom CH), 131.46 (C), 134.55 (Arom CH), 166.28 (CO_2Me), 166.62 (CO_2Me), 167.83 (NC=O), 169.48 ($OC(O)CH_3$); *m/z* (CI) 350.1 (MH^+, 100%).



Methyl-(2*R*,3*S*,4*S*)-3-(acetyloxy)-4-phthaloyl-2-methyl-4-phenylbutanoate 174.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a cream foam (0.090g, 26%) **171** $[\alpha]_D^{31}$ +40.0 (*c* 1.2 in $CHCl_3$), **ent-171** $[\alpha]_D^{34}$ –46.0 (*c* 1 in $CHCl_3$); (Found MH^+, 396.1459. $C_{22}H_{21}NO_6$ requires MH^+, 396.1447); ν_{max}/cm^{-1} 2951 (CH), 1746 (C=O), 1714 (NC=O); δ_H(400MHz; $CDCl_3$) 1.21 (3H, d, *J* 7.0 $CHCH_3$), 1.89 (3H, s $OC(O)CH_3$), 2.82 (1H, m $CHCH_3$), 3.62 (3H, s CO_2CH_3), 5.82 (1H, d, *J* 11.0 CHN), 6.49 (1H, dd, *J* 2.1 and 11.0 CHO), 7.25-7.38 (3H, m Arom H), 7.67-7.86 (6H, m Arom H); δ_C(400MHz; $CDCl_3$) 13.48 (CH_3), 20.75 (CH_3), 40.87 ($CHCH_3$), 51.75 (CH_3), 56.21 (CHN), 72.38 (CHO), 123.38 (Arom CH), 126.97 (Arom CH), 128.82 (Arom CH), 130.08 (Arom CH), 131.52 (C), 134.08 (Arom CH), 135.56 (C), 167.88 (CO_2Me), 169.89 (CO_2Me), 172.01 ($OC(O)CH_3$); *m/z* (FAB+) 396.2 (MH^+, 87%), 336(100).



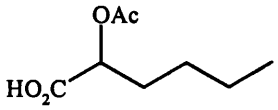
1,5-Dimethyl-3-*O*-acetyl-2,4-dideoxy-4-phthaloyl-2-methyl-*D*-xylarate 175.

The general procedure (3) for the oxidative cleavage of phenyl rings was followed to give the crude methyl ester product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a straw coloured oil (0.023g, 7%) **172** $[\alpha]_D^{32}$ +43.0 (*c* 1 in $CHCl_3$), **ent-172** $[\alpha]_D^{34}$ –52.0 (*c* 1 in $CHCl_3$); (Found MH^+, 378.1204. $C_{19}H_{19}NO_8$ requires MH^+, 378.1189); ν_{max}/cm^{-1} 2951 (CH), 1748 (NC=O), 1720 (C=O); δ_H(400MHz; $CDCl_3$) 1.29 (3H, d, *J* 7.0 CH_3), 1.86 (3H, s CH_3), 3.22 (1H, m C*H*CH_3), 3.73 (3H, s CH_3), 3.74 (3H, s CH_3), 5.43 (1H, d, *J* 7.0 CHN), 5.82 (1H, dd, *J* 4.9 and 7.0 CHO), 7.76 (2H, dd, *J* 3.05 and 5.2 Arom H), 7.87 (2H, dd, *J* 3.05 and 5.2 Arom H); δ_C(400MHz; $CDCl_3$) 13.89 (CH_3), 20.46 (CH_3), 41.44 (CH*C*H_3), 51.68 (CH_3), 51.99 (CH_3), 52.96 (CHN), 71.74 (CHO), 123.55 (Arom CH), 131.52 (C), 134.41 (Arom CH), 167.06 (CO_2Me), 167.40 (CO_2Me), 169.56 (NC=O), 172.73 (OC(O)CH_3); *m/z* (FAB+) 378.2 (MH^+, 27%), 97(100).

General procedure (4) for oxidation of aromatic compounds to carboxylic acids.

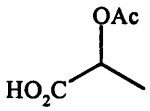
To the aromatic substrate (1 mmol) in a wide neck flask was added ethyl acetate ($8.5cm^3$), acetonitrile ($8.5cm^3$), water ($13cm^3$) and $NaIO_4$ (17 mmol). The mixture was stirred at room temperature for 10 minutes and then $RuCl_3.H_2O$ (0.020 mmol)

was added and stirred vigorously for 48 hours. The reaction mixture was diluted with ethyl acetate ($40cm^3$) and H_2O ($100cm^3$) and the organic layer separated. The aqueous was back-extracted with ethyl acetate ($20cm^3$x4) and to the combined ethyl acetate fractions was added diethyl ether ($60cm^3$) and allowed to stand for 30 minutes to precipitate RuO_2, before being dried ($MgSO_4$) then filtered through a pad of Celite and concentrated *in vacuo* to give the crude product, which was purified by bulb-to-bulb distillation under reduced pressure.



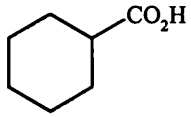
2-(Acetyloxy)hexanoic acid 182.

The general procedure (4) for the preparation of carboxylic acids was followed to give a straw coloured oil (0.375g, 87%) δ_H(270MHz; $CDCl_3$) 0.92 (3H, t, *J* 7.15 CH_2CH_3), 1.38 (4H, m CH_2CH_2), 1.88 (2H, m CH_2), 2.15 (3H, s $COCH_3$), 5.00 (1H, t, *J* 6.8 CHO), 10.11 (1H, s CO_2H). Identical to the literature data.[136]



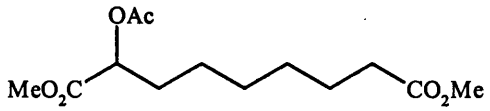
2-(Acetyloxy)propanoic acid 184.

The general procedure (4) for the preparation of carboxylic acids was followed to give a straw coloured oil (0.198g, 60%) δ_H(270MHz; $CDCl_3$) 1.54 (3H, d, *J* 7.15 CH_3), 2.14 (3H, s $COCH_3$), 5.10 (1H, q, *J* 7.15 and 14.3 CHO), 9.06 (1H, s CO_2H). Identical to the literature data.[141]



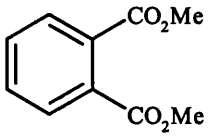
Cyclohexane carboxylic acid 185.

The general procedure (4) for the preparation of carboxylic acids was followed to give a yellow oil (0.230g, 72%) δ_H(270MHz; $CDCl_3$) 1.27 (3H, m CH_2CH), 1.42 (2H, m CH_2), 1.66 (1H, m CH), 1.75 (2H, m CH_2), 1.91(2H, m CH_2), 2.33 (1H, m $CHCO_2H$). Identical to the literature data.[137]



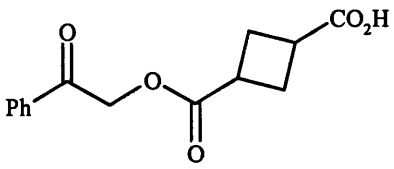
Dimethyl-2-(acetyloxy)nonanedioate 183.

The general procedure (3) for the preparation of dimethyl esters from aromatic substrates was followed to give a straw coloured oil (0.142g, 66%) δ_H(270MHz; $CDCl_3$) 1.43 (2H, m CH_2), 1.66 (2H, m CH_2), 1.85 (2H, m CH_2), 2.14 (3H, s $COCH_3$), 2.33 (2H, t, *J* 7.6 $CHOCH_2$), 3.67 (3H, s CO_2CH_3), 3.74 (3H, s CO_2CH_3), 4.99 (1H, t, *J* 6.7 CHO). Identical to the literature data.[141]



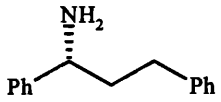
Dimethyl phthalate 186.

The general procedure (3) for the preparation of dimethyl esters from aromatic substrates was followed to give a colourless crystalline solid (0.073g, 43%) δ_H(270MHz; $CDCl_3$) 3.88 (3H, s CH_3), 3.90 (3H, s CH_3), 7.25-7.78 (4H, m Arom H). Identical to the literature data.[136]



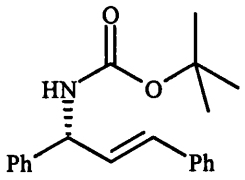
3-[(Phenacyl)carboxy]cyclobutane carboxylic acid 187.

The general procedure (4) for the preparation of carboxylic acids from aromatic substrates was followed to give a colourless crystalline solid (0.101g, 44%) δ_H(400MHz; $CDCl_3$) 2.68 (4H, m CH_2 x2), 3.31 (1H, m $CHCO_2C$), 3.42 (1H, m $CHCO_2H$), 5.37 (2H, d, *J* 7.7 CH_2), 7.49 (2H, m Arom H), 7.62 (1H, m Arom H), 7.91 (2H, m Arom H). Identical to the literature data.[167]



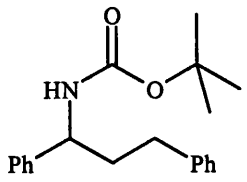
(1*R*)-Diphenyl-1-propanamine 188.

To alkene **92** (0.630g, 1.86mmol) in a solvent mix of methanol ($13cm^3$) and THF ($10cm^3$) was added $H_2NNH_2.H_2O$ ($0.8cm^3$) and the reaction mixture stirred at room temperature for 18 hours before the solvent was remove *in vacuo* to leave a white solid. The residue was suspended in 10% aqueous HCl for 10 minutes then filtered. The filtrate was neutralized with aqueous NaOH followed by extraction with dichloromethane ($20cm^3$x6). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to the give the *title compound* without further purification (0.350g, 92%) ν_{max}/cm^{-1} 3361 (NH), 3082, 3060, 3025, 2934 and 2856 (CH), 1602 (NH); δ_H(270MHz; $CDCl_3$) 1.72 (2H, s NH_2), 1.99 (2H, m CH_2Ph), 2.60 (2H, m CH_2CHN), 3.89 (1H, t, *J* 6.8 CHN), 7.14-7.41 (10H, m Arom H); *m/z* (CI) 212.1 (MH^+, 12%), 194(8), 132.1(7), 119(10), 106(100).



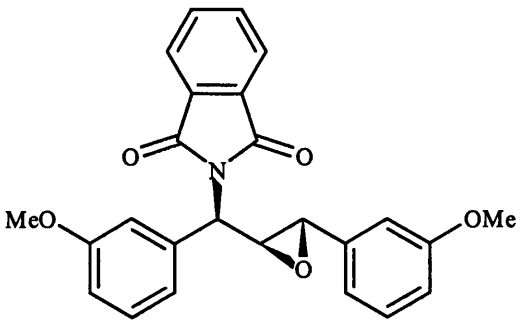
***tert*Butyl(1*R*,2*E*)-1,3-diphenyl-2-propenyl carbamate 189.**

To alkene **92** (0.540g, 1.590mmol) in a solution mix of THF (5cm^3) and ethanol (3cm^3) was added $H_2NNH_2.H_2O$ (0.088g, 1.752mmol) and stirred at room temperature for 72 hours. Di-*tert*butyl dicarbonate (1.039g, 4.77mmol) was added at room temperature and stirred for another 4 hours. The mixture was diluted with dichloromethane (10cm^3) and water (15cm^3) and the organic fraction separated. The aqueous fraction was back-extracted with dichloromethane (10cm^{3}x4) and the combined dichloromethane fractions dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel chromatography to give the *title compound* as white needles (0.340g, 69%) (Found: C, 77.7; H, 7.6; N, 4.6. $C_{20}H_{23}NO_2$ requires C, 77.6; H, 7.5; N, 4.5%); δ_H(400MHz; $CDCl_3$) 1.45 (9H, s 3xCH_3), 4.96 (1H, m CHN), 5.45 (1H, m CHN), 6.31 (1H, dd, *J* 5.9 and 15.75 CH=C*H*Ph), 6.54 (1H, d, *J* 15.75 C*H*=CHPh), 7.24-7.38 (10H, m Arom H); δ_C(400MHz; $CDCl_3$) 28.44 (CH_3x3), 56.73 (CHN), 79.81 (C), 126.59 (Arom CH), 127.02 (Arom CH), 127.55 (Arom CH), 127.71 (Arom CH), 128.57 (Arom CH), 128.75 (Arom CH), 129.83 (Arom CH), 131.15 (Arom CH), 136.78 (C), 141.57 (C), 155.07 ($NCO_2C(CH_3)_3$); *m/z* (CI) 310.0 (MH^+, 27%), 279(21), 254(98), 193(91), 150(100).



***tert*Butyl(1*R*,2*E*)-1,3-diphenylpropyl carbamate 190.**

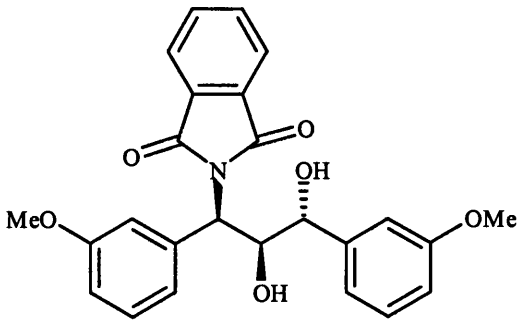
To alkene **186** (0.140g, 0.454mmol) in ethyl acetate ($5cm^3$) was added 10% palladium-carbon (0.010g) and stirred vigorously for 48 hours at room temperature under an atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give the *title compound* without purification as a white solid (0.140g, 100%) $[\alpha]_D^{30}$ –1 (*c* 1 in $CHCl_3$); δ_H(270MHz; $CDCl_3$) 1.42 (9H, s $3xCH_3$), 2.06 (2H, m CH_2), 2.63 (2H, m CH_2), 4.68 (1H, m CHN), 4.83 (1H, m CHN), 7.14-7.35 (10H, m Arom H); δ_C(270MHz; $CDCl_3$) 28.38 ($3xCH_3$), 32.57 (CH_2), 38.58 (CH_2), 54.71 (CHN), 77.34 (C), 123.18 (Arom CH), 125.94 (Arom CH), 126.40 (Arom CH), 127.28 (Arom CH), 128.36 (Artom CH), 128.41 (Arom CH), 128.63 (Arom CH), 134.30 (C), 141.45 (C), 154.70 ($NCO_2C(CH_3)_3$).



Phthaloyl-{(*R*)-(3-methoxyphenyl)[(2*S*,3*S*)-3-(3-methoxyphenyl)oxiranyl] methane 191.

To alkene **81** (0.50g, 1.253mmol) in dichloromethane ($30cm^3$) at 0 °C was added *m*CPBA (0.395g, 1.378mmol) and the reaction stirred at 0 °C for 3 hours followed

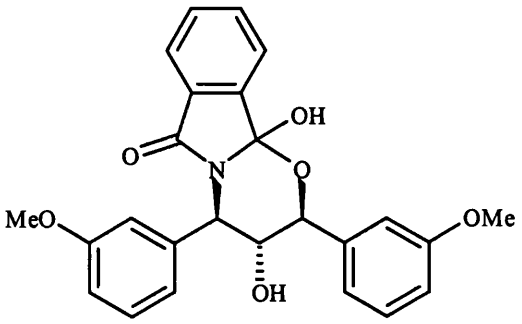
by stirring at room temperature for 16 hours. Diluted with dichloromethane ($30cm^3$) and saturated aqueous sodium hydrogen carbonate ($50cm^3$) and vigorously stirred for 30 minutes. The organic layer was separated and the aqueous back-extracted with dichloromethane ($4x20cm^3$). The combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a cream gum (0.390g, 75%) (Found MH^+, 416.1496. $C_{25}H_{21}NO_5$ requires MH^+, 416.1497); δ_H(270MHz; $CDCl_3$) 3.75 (3H, s CH_3), 3.79 (3H, s CH_3), 3.93 (1H, d, *J* 2.0 CHO), 4.18 (1H, dd, *J* 2.0 and 8.2 CHO), 5.13 (1H, d, *J* 8.2 CHN), 6.81-7.29 (8H, m Arom H), 7.71-7.76 (2H, m Arom H), 7.85-7.89 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 55.60 (2xOCH_3), 57.53 (CHN), 60.06 (CHO), 60.86 (CHO), 110.85 (Arom CH), 113.56 (Arom CH), 113.70 (Arom CH), 114.60 (Arom CH), 118.44 (Arom CH), 119.78 (Arom CH), 123.60 (Arom CH), 123.72 (Arom CH), 129.83 (Arom CH), 130.12 (Arom CH), 131.90 (C), 134.34 (Arom CH), 134.48 (Arom CH), 137.50 (C), 137.78 (C), 159.90 ($COCH_3$), 159.98 ($COCH_3$), 168.24 (NC=O); *m/z* (FAB+) 416.2 (MH^+, 63%), 397.1(25), 266.1(100).



(1*R*,2*S*,3*R*)-2,3-dihydroxy-1,3-bis(3-methoxyphenyl)propane 193.

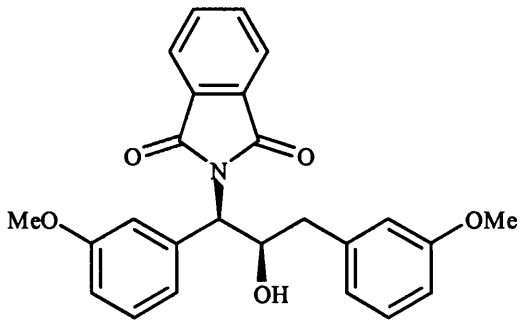
To the epoxide **188** (1.090g, 2.626mmol) in THF ($50cm^3$) was added 1M H_2SO_4 ($2.62cm^3$) and stirred at room temperature for 48 hours. The mixture was diluted

with dichloromethane ($50cm^3$) and saturated aqueous sodium hydrogen carbonate ($100cm^3$) and stirred vigorously for 30 minutes. The organic fraction was separated and the aqueous back-extracted with dichloromethane ($5x30cm^3$). The combined dichloromethane fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 4:6) to give compounds **193** and **194**. The diol **193** was isolated as a white foam (0.470g, 42%) $[\alpha]_D^{33}$ +6.5 (*c* 2 in $CHCl_3$); (Found MH^+, 434.1589. $C_{25}H_{24}NO_6$ requires MH^+, 434.1600); ν_{max}/cm^{-1} 3455 (OH), 3058, 3002, 2940 and 2835 (CH), 1769 and 1705 (NC=O); δ_H(400MHz; $CDCl_3$) 1.63 (1H, s OH), 2.54 (1H, s OH), 3.76 (3H, s CH_3), 3.77 (3H, s CH_3), 4.61 (1H, d, *J* 5.3 CHO), 4.99 (1H, m CHO), 5.37 (1H, d, *J* 7.0 CHN), 6.76-6.89 (4H, m Arom H), 6.98-7.06 (2H, m Arom H), 7.18-7.27 (2H, m Arom H), 7.70 (2H, m Arom H), 7.80 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 55.48 (OCH_3), 55.56 (OCH_3), 56.90 (CHN), 74.56 (CHO), 75.43 (CHO), 112.88 (Arom CH), 113.83 (Arom CH), 114.13 (Arom CH), 114.47 (Arom CH), 119.81 (Arom CH), 121.00 (Arom CH), 123.65 (Arom CH), 129.56 (Arom CH), 129.89 (Arom CH), 131.82 (C), 134.34 (Arom CH), 138.39 (C), 141.28 (C), 159.57 ($COCH_3$), 159.77 ($COCH_3$), 169.14 (NC=O); *m/z* (FAB+) 434.1 (MH^+, 64%), 416.1(21), 398.1(18), 296.1(54), 266.1(100).



(2*S*,3*R*,4*R*)-3-Hydroxy-2,4-bis(3-methoxyphenyl)-10b-methyl-3,4-dihydro-2*H*[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one 194.

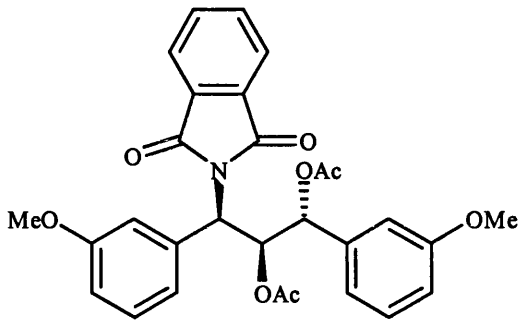
Isolated as a white gum (0.080g, 7%) δ_H(400MHz; $CDCl_3$) 3.70 (3H, s CH_3), 3.79 (3H, s CH_3), 4.65 (1H, d, *J* 5.0 CH_aO), 4.89 (1H, d, *J* 5.0 CH_bO), 5.14 (1H, m CH_aO), 5.15 (1H, dd, *J* 5.0 and 7.3 CH_bO), 5.37 (1H, d, *J* 8.8 CHN), 5.63 (1H, d, *J* 7.3 CHN), 6.41 (1H, m Arom H), 6.59 (1H, m Arom H), 6.80-7.31 (7H, m Arom H), 7.61-7.83 (4H, m Arom H); δ_C(400MHz; $CDCl_3$) 55.47 (CH_3), 55.57 (CH_3), 56.96 (CHN), 72.66 (CHO), 74.66 (CHO), 111.15 (Arom CH), 113.39 (Arom CH), 114.14 (Arom CH), 115.18 (Arom CH), 118.85 (Arom CH), 121.89 (Arom CH), 123.20 (Arom CH), 123.41 (Arom CH), 129.39 (Arom CH), 129.93 (Arom CH), 130.16 (Arom CH), 131.67 (C), 133.97 (C), 134.18 (Arom CH), 134.30 (Arom CH), 138.37 (C), 141.58 (C), 159.34 (*C*OCH_3), 159.83 (*C*OCH_3), 168.38 (NC=O); *m/z* (FAB+) 434.1 (MH^+, 42%), 416.0(27), 296.0(26), 279.1(25), 266.0(100).



(1*R*,2*R*)-1-Phthaloyl-2-hydroxy-1,3-bis(3,methoxyphenyl)propane 195.

In a sealed vessel was placed epoxide **185** (0.270g, 0.651mmol), ethyl acetate ($10cm^3$) and 10% palladium on carbon (0.020g). The vessel was placed under vacuum and hydrogen introduced. The mixture was then stirred vigorously at room temperature for 72 hours with a balloon of hydrogen applying atmospheric pressure. The reaction mixture was filtered through a pad of Celite and washed with ethyl acetate ($40cm^3$). The solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a cream gum, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2) to give the *title compound* as a colourless oil (0.050g, 18%) (Found MH^+, 418.1659. $C_{25}H_{23}NO_5$ requires MH^+, 418.1654); ν_{max}/cm^{-1} 3467 (OH), 2924 and 2836 (CH), 1769 and 1708 (NC=O); δ_H(400MHz; $CDCl_3$) 1.26 (1H, s OH), 2.61 (1H, dd, *J* 9.1 and 13.8 CH_2), 2.80 (1H, dd, *J* 3.5 and 13.8 CH_2), 3.77 (3H, s CH_3), 3.81 (3H, s CH_3), 5.07 (1H, dt, *J* 3.5 and 9.1 CHO), 5.26 (1H, d, *J* 9.1 CHN), 6.71-6.79 (3H, m Arom H), 6.85 (1H, m Arom H), 7.14-7.22 (3H, m Arom H), 7.25-7.31 (1H, m Arom H), 7.67 (2H, m Arom H), 7.79 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 41.86 (CH_2), 55.50 (OCH_3), 55.62 (OCH_3), 60.99 (CHN), 71.40 (CHO), 112.32 (Arom CH), 113.94 (Arom CH), 114.72 (Arom CH), 115.28 (Arom CH), 121.29 (Arom CH), 121.91 (Arom CH), 123.57 (Arom CH), 129.75 (Arom CH), 130.11 (Arom CH), 131.98 (C), 134.25 (Arom CH), 139.10 (C), 139.48 (C), 159.81 (*C*OCH_3), 159.98

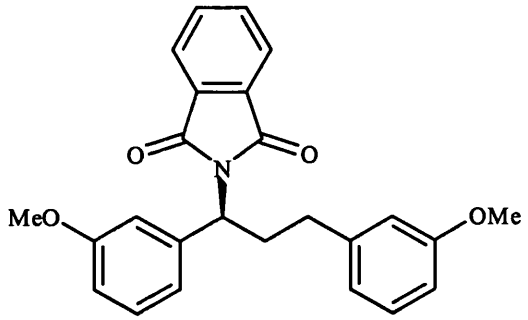
($COCH_3$), 168.97 (NC=O); *m/z* (FAB+) 418.1 (MH^+, 69%), 253.1(63), 173.1(65), 97.1(100).



(1*R*,2*S*,3)-3-Phthaloyl-2-isopropenyloxy-1,3-bis(3-methoxyphenyl)propyl acetate 196.

To diol **193** (1.120g, 2.59mmol) in dichloromethane ($25cm^3$) was added Et_3N ($0.701cm^3$, 5.43mmol) and 4-(dimethylamino)pyridine (0.010g) and cooled to 0°C. Ac_2O ($0.975cm^3$, 10.35mmol) was added and stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane ($20cm^3$) and saturated aqueous hydrogen carbonate ($50cm^3$) and stirred vigorously for 30 minutes. The organic fraction was separated and the aqueous back-extracted with dichloromethane ($30cm^3$x3). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 7:3) to yield *the title compound* as a white foam (1.216g, 91%) $[\alpha]_D^{31}$-72 (*c* 2 in $CHCl_3$); ν_{max}/cm^{-1} 2924 and 2837 (CH), 1759 and 1715 (NC=O), 1749 (C=O); (Found M^+, 517.1738. $C_{29}H_{27}NO_8$ requires M^+, 517.1737); δ_H(400MHz; $CDCl_3$) 1.93 (3H, s CH_3), 2.05 (3H, s CH_3), 3.74 (3H, s OCH_3), 3.80 (3H, s OCH_3), 5.22 (1H, d, *J* 10.8 CHN), 5.95 (1H, d, *J* 3.2 CHO), 6.62 (1H, t, *J* 2.0 CHO), 6.73-6.85 (4H, m Arom H), 7.12-7.26 (4H, m Arom H), 7.65 (2H, dd, *J* 2.9 and 5.6 Arom H), 7.76

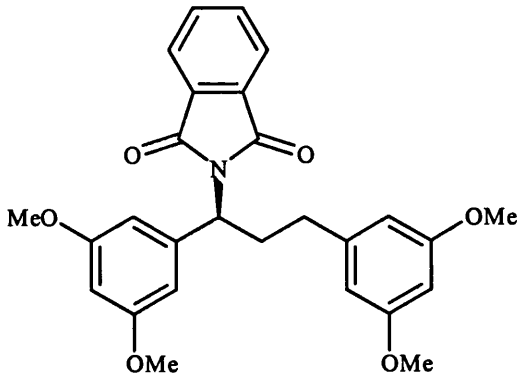
(2H, dd, *J* 2.9 and 5.6 Arom H); δ_C(400MHz; $CDCl_3$) 21.22 (CH_3), 21.34 (CH_3), 55.28 (CHN), 55.46 (OCH_3), 55.64 (OCH_3), 71.53 (CHO), 74.50 (CHO), 113.79 (Arom CH), 114.38 (Arom CH), 114.98 (Arom CH), 115.44 (Arom CH), 120.52 (Arom CH), 122.49 (Arom CH), 123.60 (Arom CH), 129.36 (Arom CH), 129.89 (Arom CH), 131.65 (C), 134.24 (Arom CH), 136.11 (C), 136.29 (C), 159.30 ($COCH_3$), 159.79 ($COCH_3$), 167.65 (NC=O), 169.72 ($C(O)CH_3$), 169.84 ($C(O)CH_3$); *m/z* (EI) 517.1 (M^+, 14%), 415.1(36), 397.1(15), 296.1(23), 266.1(100).



(1*S*)-1-Phthaloyl-1,3-bis(3-methoxyphenyl)propane 197.

To alkene **81** (0.400g, 1.0mmol) was added ethyl acetate ($10cm^3$) and 10% palladium on carbon (0.010g). The atmosphere was evacuated and hydrogen was introduced *via* a balloon and the mixture stirred vigorously for 24 hours. Reaction mixture was filtered through a pad of Celite and washed with ethyl acetate ($100cm^3$), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a straw coloured oil (0.400g, 100%) $[\alpha]_D^{31}$ -14.0 (*c* 2 in $CHCl_3$); (Found M^+, 401.1617. $C_{25}H_{23}NO_4$ requires M^+, 401.1627); ν_{max}/cm^{-1} 2999, 2936 and 2835 (CH), 1770 and 1709 (NC=O); δ_H(270MHz; $CDCl_3$) 2.64 (3H, m CH_2 and 1xCH_2), 3.01 (1H, m 1xCH_2), 3.75

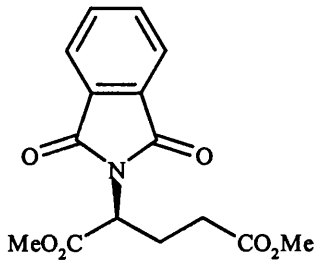
(3H, s OCH_3), 3.78 (3H, s OCH_3), 5.33 (1H, dd, *J* 5.9 and 10.1 CHN), 6.60-6.82 (4H, m Arom H), 7.10 (3H, m Arom H), 7.22 (1H, m Arom H), 7.65 (2H, dd, *J* 2.9 and 5.7 Arom H), 7.76 (2H, dd, *J* 2.9 and 5.7 Arom H); δ_C(400MHz; $CDCl_3$) 32.25 (CH_2), 33.48 (CH_2), 54.70 (CHN), 55.00 (OCH_3), 55.17 (OCH_3), 111.39 (Arom CH), 113.27 (Arom CH), 113.74 (Arom CH), 113.94 (Arom CH), 120.36 (Arom CH), 120.73 (Arom CH), 123.05 (Arom CH), 129.30 (Arom CH), 129.48 (Arom CH), 131.76 (C), 133.79 (Arom CH), 141.12 (C), 142.37 (C), 159.51 (OCH_3), 159.64 (OCH_3), 168.24 (NC=O); *m/z* (EI) 401.2 (M^+, 100%).



(1*S*)-1-Phthaloyl-1,3-bis(3,5-dimethoxyphenyl)propane 198.

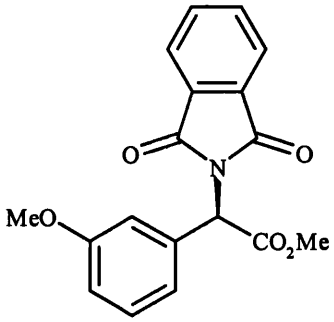
To alkene **82** (2.00g, 3.27mmol) was added ethyl acetate ($30cm^3$) and 10% palladium on carbon (0.030g). The atmosphere was evacuated and hydrogen was introduced *via* a balloon and the mixture stirred vigorously for 24 hours. Reaction mixture was filtered through a pad of Celite and washed with ethyl acetate ($200cm^3$), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ether 7:3) to give the *title compound* as a straw coloured oil (2.010g, 100%) $[\alpha]_D^{32}$ –7.0 (*c* 2 in $CHCl_3$); (Found M^+, 461.1837. $C_{27}H_{27}O_6N$ requires M^+, 461.1838); ν_{max}/cm^{-1} 3000, 2938 and 2837 (CH), 1770 and 1708 (NC=O); δ_H(400MHz; $CDCl_3$) 2.52 (1H, m CH_2), 2.63 (2H, m CH_2), 3.00 (1H, m CH_2),

3.73 (3H, s OCH_3), 3.77 (3H, s OCH_3), 5.28 (1H, dd, *J* 5.9 and 10.2 CHN), 6.14 (1H, t, *J* 2.3 Arom H), 6.29 (2H, d, *J* 2.0 Arom H), 6.36 (1H, t, *J* 2.3 Arom H), 6.71 (2H, d, *J* 2.3 Arom H), 7.70 (2H, m Arom H), 7.76 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 32.39 (CH_2), 34.28 (CH_2), 55.25 (CHN), 55.50 (OCH_3), 55.68 (OCH_3), 98.26 (Arom CH), 100.06 (Arom CH), 106.35 (Arom CH), 106.58 (Arom CH), 123.23 (Arom CH), 131.90 (C), 133.98 (Arom CH), 142.08 (C), 143.21 (C), 160.70 ($COCH_3$), 160.86 ($COCH_3$), 168.37 (NC=O); *m/z* (FAB+) 462.2 (MH^+, 100%).



Dimethyl-(2*S*)-2-phthaloylpentaedioate 199.

The general procedure (3) for the preparation of dimethyl esters from aromatic substrates was followed to give a straw coloured oil (0.118g, 41%) $[\alpha]_D^{29}$ (*c* 1 in $CHCl_3$); (Found MH^+, 306.0975. $C_{15}H_{15}NO_6$ requires MH^+, 306.0977); ν_{max}/cm^{-1} 2954 (CH), 1776 and 1716 (NC=O) 1738 (CO_2CH_3); δ_H(270MHz; $CDCl_3$) 2.41 (2H, m CH_2), 2.52 (1H, m CH_2), 2.62 (1H, m CH_2), 3.62 (3H, s CH_3), 3.75 (3H, s CH_3), 4.94 (1H, dd, *J* 5.3 and 10.25 CHN), 7.77 (2H, dd, *J* 3.1 and 5.7 Arom H), 7.88 (2H, dd, *J* 3.1 and 5.7 Arom H); δ_C(270MHz; $CDCl_3$) 24.65 (CH_2), 30.99 (CH_2), 51.46 (CHN), 52.12 (CH_3), 53.20 (CH_3), 123.82 (Arom CH), 131.87 (C), 134.49 (Arom CH), 167.62 (C=O), 169.33 (CO_2CH_3), 172.70 (CO_2CH_3); *m/z* (FAB+) 306.1 (MH^+, 100%).



Methyl-(2R)-(phthaloyl)(3-methoxyphenyl) ethanoate 200.

Method A: To a solvent mix of ethyl acetate ($3cm^3$), acetonitrile ($3cm^3$) and water ($5cm^3$) was added the alkene **81** (0.200g, 0.436mmol) and sodium periodate (0.450g, 2.105mmol) and stirred for 10 minutes. The ruthenium trichloride hydrate (0.002g, 0.010mmol) was added and the mixture stirred vigorously with water cooling for 48 hours before being diluted with ethyl acetate ($30cm^3$) and water ($50cm^3$). The organic layer was separated and the aqueous back-extracted with ethyl acetate ($5x20cm^3$) and the combined organic fractions diluted with diethyl ether ($30cm^3$), filtered through a pad of Celite, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. The crude product was dissolved in ethanol ($10cm^3$) and methylated with diazomethane (generated from diazald®/KOH) to give the crude methyl ester product. Purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2).

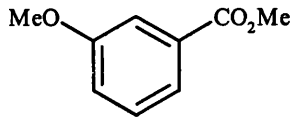
Method B: To a solvent mix of dichloromethane ($11cm^3$) and 2.5 M sodium methoxide ($2.75cm^3$) was added the alkene **81** (0.315g, 0.686mmol) and stirred at –78 °C. Ozone was bubbled through the mixture at –78 °C for 1 hour or until a blue colour persisted in the solution. The reaction mixture was then flushed with oxygen until no blue colour was seen and warmed to room temperature and diluted with dichloromethane ($10cm^3$) and water ($20cm^3$). The dichloromethane

layer was separated and the aqueous back-extracted with dichloromethane ($4x20cm^3$). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ethyl acetate 8:2).

Method C: The alkene (0.250g, 0.626mmol) in dichloromethane ($20cm^3$) was cooled to –78 °C and ozone passed through the solution for 30 minutes or until a blue colour persisted. The reaction mixture was then flushed with oxygen until no blue colour was visable and allowed to warm to room temperature. Aqueous 30% hydrogen peroxide ($2cm^3$) was then added and the mixture heated to reflux for 1 hour before being diluted with dichloromethane ($10cm^3$) and water ($20cm^3$). The organic layer was separated and the aqueous back-extracted with dichloromethane ($4x20cm^3$) and the combined organic fractions dried ($MgSO_4$) and concentrated *in vacuo* to give the crude carboxylic acid, which was then dissolved in ethanol ($10cm^3$) and treated with diazomethane (generated from diazald®/KOH) to give the crude methyl ester. Purified by silica gel column chromatography using (light petroleum/ ethyl acetate 8:2).

Compound **197** was isolated as a cream coloured foam (0.113g, 56%) (Found MH^+, 326.1040. $C_{18}H_{15}NO_5$ requires MH^+, 326.1030); ν_{max}/ cm^{-1} 2924 and 2836 (CH), 1774 and 1715 (NC=O); δ_H(400MHz; $CDCl_3$) 3.80 (3H, s OCH_3), 3.81 (3H, s OCH_3), 5.99 (1H, s CHN), 6.87 (1H, m Arom H), 7.12 (2H, m Arom H), 7.26 (1H, m Arom H), 7.72 (2H, m Arom H), 7.85 (2H, m Arom H); δ_C(400MHz; $CDCl_3$) 53.41 (CH_3), 55.61 (CH_3), 56.08 (CHN), 114.50 (Arom CH), 115.53 (Arom CH), 122.16 (Arom CH), 123.73 (Arom CH), 123.83 (Arom CH), 129.73

(Arom CH), 131.95 (Arom CH), 132.85 (C), 134.42 (Arom CH), 135.92 (C), 159.70 ($COCH_3$), 167.16 (NC=O), 168.52 (CO_2Me); *m/z* (CI) 326.0 (MH^+, 7%), 310.0(100).



Methyl-3-methoxybenzoate 202.

A cream solid (0.064g, 62%) ν_{max}/cm^{-1} 3003, 2952 and 2838 (CH), 1722 (C=O); δ_H(270MHz; $CDCl_3$) 3.84 (3H, s CH_3), 3.91 (3H, s CH_3), 7.10 (1H, m Arom H), 7.34 (1H, m Arom H), 7.55 (1H, m Arom H), 7.63 (1H, m Arom H); δ_C(400MHz; $CDCl_3$) 52.49 (CH_3), 55.72 (CH_3), 114.16 (Arom CH), 119.67 (Arom CH), 122.15 (Arom CH), 129.54 (Arom CH), 131.60 (C), 159.65 (C), 167.05 (C); *m/z* (EI) 166.1 (M^+, 70%), 135.1(100).

7 References

1. J. Tsuji; *Organic Synthesis with Palladium Compounds*, Springer, Heidelberg, **1980**; K. Januszkiewicz and H. Alper; *Tetrahedron Lett.*, **1983**, *24*, 5159, and references therein.
2. R. F. Heck; *Org. React.*, **1983**, *27*, 1.
3. J. K. Stille; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508.
4. N. Miyaura, T. Yanagi and A. Suzuki; *Synth. Commun.*, **1981**, *11*, 513; N. Miyaura and A. Suzuki; *Chem. Rev.*, **1995**, *95*, 2457.
5. C. G. Frost, J. Howarth and J. M. J. Williams; *Tetrahedron: Asymmetry*, **1992**, *3*, 1089; B. M. Trost and D. L. Van Vranken; *Chem Rev.*, **1996**, *96*, 395.
6. J. Tsuji, H. Takashashi and M. Morikawa; *Tetrahedron Lett.*, **1965**, 4387.
7. J. P. Genêt, M. Balabane and J. E. Bäckvall, J. E. Nyström; *Tetrahedron Lett.*, **1983**, *24*, 2745.
8. M. J. Brown, E. J. McIntyre; *J. Chem. Soc., Perkin Trans. 2*, **1985**, 961.
9. B. Bhatia, M. M. Reddy, J. Iqbal; *Tetrahedron Lett.*, **1993**, *34*, 6301; Y. Xu, B. Zhou; *J. Org. Chem.*, **1987**, *52*, 974.
10. B. M. Trost, C. A. Merlic; *J. Am. Chem. Soc.*, **1990**, *112*, 9590.
11. I. Minami, I. Shimizu, J. Tsuji; *J. Organomet. Chem.*, **1985**, *296*, 269.
12. R. Takeuchi, M. Kashio; *J. Am. Chem. Soc.*, **1998**, *120*, 8647; R. Takeuchi, M. Kashio; *Angew. Chem. Int. ed. Engl.*, **1997**, *36*, 263.
13. A. Indolese, G. Consiglio; *Organometallics*, **1994**, *13*, 2230.
14. B. M. Trost, M–H. Hung; *J. Am. Chem. Soc.*, **1983**, *105*, 7757; G. C. Lloyd-Jones, A. Pfaltz; *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 462.
15. S. M. Roberts, G. T. Woolley and R. F. Newton; *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1729.
16. S. K. Kang, D. Y. Kim, R. K. Hong and P. S. Ho; *Synthetic Commun.*, **1996**, *26*, 1729.
17. B. M. Trost; *Tetrahedron*, **1977**, *33*, 2615.
18. S. I. Murahashi, Y. Taniguchi, Y. Imada and Y. Tanigawa; *J. Org. Chem*, **1989**, *54*, 3292; S. E. Byström, R. Aslanian and J. E. Bäckvall; *Tetrahedron Lett.*, **1985**, *26*, 1749; P. von Matt, O. Loiseleur, G. Koch, A.

Pfaltz and C. Lefeber, T. Feucht and G. Helmchen; *Tetrahedron: Asymmetry*, **1994**, *5*, 573; U. Burckhardt, M. Baumann, G. Trabesinger, V. Gramlich and A. Tongi; *Organometallics*, **1997**, *16*, 5252; R. Jumnah, A. C. Williams and J. M. J. Williams; *Tetrahedron Lett.*, **1993**, *34*, 6619.

19. M. Julia, M. Nei and L. Saussime; *J. Organomet. Chem.*, **1979**, *181*, C17.
20. J. Tsuji, K. Sakia, H. Nagashima and I. Shimizu; *Tetrahedron Lett.*, **1981**, *22*, 131; R. C. Larock, L.W. Harrison and M. H. Hsu; *J. Org. Chem.*, **1984**, *49*, 3662.
21. B. Åkermark, J. E. Nystrom, T. Rein, J. E. Bäckvall, P. Helquist and R. Aslanian; *Tetrahedron Lett.*, **1984**, *25*, 5719.
22. B. M. Trost, J. Yashida and M. Lautens; *J. Am. Chem. Soc.*, **1983**, *105*, 4494.
23. N. Miyaura, T. Yano and A. Suzuki; *Tetrahedron Lett.*, **1980**, *21*, 2865.
24. J. Tsuji, I. Minami, I. Shimizu; *Synthesis*, **1986**, 623; J-Y. Legrosand J-C. Fiaud; *Tetrahedron Lett.*, **1990**, *31*, 7453.
25. J-Y. Legros and J-C. Fiaud; *Tetrahedron Lett.*, **1990**, *31*, 7453.
26. L. Zhu, R. M. Wehmeyer and R. D. Rieke; *J. Org. Chem.*, **1991**, *56*, 1445; T. Hayashi, A. Yamamoto and T. Hagihara; *J. Org. Chem.*, **1986**, *51*, 723.
27. T. Hayashi, M. Konishi, K. Yokota and M. Kumada; *J. Chem. Soc., Chem. Commun.*, **1981**, 313.
28. J. S. Temple and J. Schwartz; *J. Am. Chem. Soc.*, **1980**, *102*, 7381.
29. J. S. Temple, M. Riediker and J. Schwartz; *J. Am. Chem. Soc.*, **1982**, *104*, 1310.
30. B. M. Trost and E. Keinan; *Tetrahedron Lett.*, **1980**, *21*, 2595; A. Gollaszewski and J. Schwartz; *Organometallics*, **1985**, *4*, 417; A. M. Echavarren, D. R. Teuting and J. K. Stille; *J. Am. Chem. Soc.*, **1988**, *110*, 4039.
31. F. M. Hauser, S. R. Ellenberger and J. P. Glusker, C. J. Smart, H. L. Carrell; *J. Org. Chem.*; **1986**, *51*, 50; J. F. Bower, R. Jumnah, A. C. Williams and J. M. J. Williams; *J. Chem. Soc., Perkin Trans. 1*; **1997**, 1411; B. M. Trost, S. R. Pulley; *J. Am. Chem. Soc.*, **1995**, *117*, 10143; B. M. Trost, R. Madsen, S. D. Guile; *Tetrahedron Lett.*, **1997**, *38*, 1707; A. L. E. Larsson, R. G. P. Gatti and J. E. Bäckvall; *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2873.

32. B. M. Trost and T. R. Verhoeven; *J. Am. Chem. Soc.*, **1978**, *100*, 3435.

33. I. C. Baldwin and J. M. J. Williams; *Tetrahedron: Asymmetry*, **1995**, *6*, 1515.

34. J. P. Genêt, M. Balabane and J. E. Bäckvall and J. E. Nyström; *Terahedron Lett.*, **1983**, *24*, 2745.

35. B. M. Trost, R. Madsen and S. D. Guile; *Tetrahedron Lett.*, **1997**, *38*, 1707.

36. M. Grellier, M. Pfeffer and G. van Koten; *Tetrahedron Lett.*, **1994**, *35*, 2877.

37. M. Toffano, J-V. Legros and J-C. Fiaud; *Tetrahedron Lett.*, **1997**, *38*, 77.

38. I. Alonso, J. C. Carretero, J. L. Garrido, V. Magro and C. Pedregal; *J. Org. Chem.*, **1997**, *62*, 5682.

39. R. O. Hutchins, J. Wei and S. J. Rao; *J. Org. Chem.*, **1994**, *59* 4007.

40. J. Tsui, I. Shimizu, I. Minami, Y. Ohashi, K. Takahashi and T. Sugiura; *J. Org. Chem.*, **1985**, *50*, 1523; J. Tsuji and I. Minami; *Acc. Chem. Res.*, **1987**, *20*, 140.

41. L. Minami, M. Yuhara and J. Tsuji; *Tetrahedron Lett.*, **1987**, *28*, 2737.

42. B. M. Trost, A. C. Krueger, R. C. Bunt and J. Zambrano; *J. Am. Chem. Soc.*, **1996**, *118*, 6520; J. Tsuji; *Tetrahedron*, **1986**, *42*, 4361.

43. B. M. Trost, N. R. Schmuff and M. J. Miller; *J. Am. Chem. Soc.*, **1980**, *102*, 5979.

44. F. L. Granberg and J. E. Bäckvall; *J. Am. Chem. Soc.*, **1992**, *114*, 6858; F. K. Sheffy and J. K. Stille; *J. Am. Chem. Soc.*, **1983**, *105*, 7173.

45. Y. Tanigawa, K. Nishimura, A. Kawasaki and S. Murahashi; *Tetrahedron Lett.*, **1982**, *23*, 5549.

46. I. Starý, I. G. Stará and P. Kocovsky; *Tetrahedron*, **1994**, *50*, 529.

47. A. L. E. Larsson, R. G. P. Gatti and J-E. Bäckvall; *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2873; R. G. P. Gatti, A. L. E. Larsson and J-E. Bäckvall; *J. Chem. Soc., Perkin Trans. 1*, **1997**, 577.

48. B. M. Trost and G. R. Cook; *Tetrahedron Lett.*, **1996**, *37*, 7485.

49. N. S. Sirisoma and P. M. Woster; *Tetrahedron Lett.*, **1998**, *39*, 1489.

50. Y. Inoue, M. Taguchi, M. Toyofuku and H. Hashimoto; *Bull. Chem. Soc. Jpn.*,**1984**, *57*, 3021.

51. R. D. Connell, T. Rein, B. Åkermark and P. Helquist; *J. Org. Chem.*, **1988**, *53*, 3845.

52. S. E. Byström, R. Aslanian and J. E. Bäckvall; *Tetrahedron Lett.*, **1985**, *26*, 1749.

53. Y. Tanigawa, K. Nishimura, A. Kawasaki and S. I. Murahashi; *Tetrahedron Lett.*, **1982**, *23*, 5549.

54. R. O. Hutchins, J. Wei, S. J. Rao; *J. Org. Chem.*, **1994**, *59*, 4007.

55. B. M. Trost and L. Weber; *J. Am. Chem. Soc.*, **1975**, *97*, 1611.

56. S. I. Murahashi, Y. Taniguchi, Y. Imada and Y. Tanigawa; *J. Org. Chem.*, **1989**, *54*, 3292.

57. K. L. Granberg and J. E. Bäckvall; *J. Am. Chem. Soc.*, **1992**, *114*, 6858.

58. G. Brenchley, E. Merifield, M. Fedouloff and M. Wills; *Tetrahedron Lett.*, **1994**, *35*, 2791; G. Brenchley, M. Fedouloff, M. F. Mahon, K. C. Molloy and M. Wills; *Tetrahedron,* **1995**, *51*, 10581.

59. H. Tye, D. Smyth, C. Eldred and M. Wills; *J. Chem. Soc., Chem. Commun.*, **1997**, 1053.

60. T. Hayashi, A. Yamamoto, Y. Ito, E. Nishioka, H. Miura and K. Yanagi; *J. Am. Chem. Soc.*, **1989**, *111*, 6301.

61. B. M. Trost and R. C. Bunt; *J. Am. Chem. Soc.*, **1994**, *116*, 4089.

62. B. Åkermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg; *Organometallics*, **1984**, *3*, 679; B. Åkermark, B. Krakenberger, A. Vitagliano; *Organometallics*, **1987**, *6*, 620.

63. G. J. Dawson, C. G. Frost, S. J. Coote and J. M. J. Williams; *Tetrahedron Lett.*, **1993**, *34*, 3149.

64. J. Sprinz, G. Helmchen; *Tetrahedron Lett.*, **1993**, *34*, 1769.

65. P. Von Matt, A. Pfaltz; *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 566.

66. A. Sudo and K. Saigo; *J. Org. Chem.*, **1997**, *62*, 5508.

67. G. J. Dawson, S. J. Coote and J. M. J. Williams; *Tetrahedron: Asymmetry*, **1995**, *6*, 2535.

68. A. Togni, U. Burckhardt, V. Gramlich, P. Pregosin and R. Salzmann; *J. Am. Chem. Soc.*, **1996**, *118*, 1031.

69. Š. Vyskocil, M. Smrcina, V. Hanuš, M. Polášek and P. Kocovský; *J. Org. Chem.*, **1998**, *63*, 7738.

70. T. Constantiex, J-M. Brunel, A. Labande and G. Buono; *Synlett*, **1998**, 49.

71. C. G. Frost, J. M. J. Williams; *Tetrahedron Lett.*, **1993**, *34*, 2015.

72. J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin and J. M. J. Williams; *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2065.

73. A. Chesney, M. R. Bryce, R. W. J. Chubb, A. S. Batsanov and J. A. K. Howard; *Tetrahedron: Asymmetry*, **1997**, *8*, 2337.

74. B. Koning, A. Meetsma and R. M. Kellogg; *J. Org. Chem.*, **1998**, *63*, 5533.

75. K. Hirio and Y. Suzuki; *Tetrahedron Lett.*, **1998**, *39*, 6499.

76. U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt and A. Pfaltz; *Tetrahedron*, **1992**, *48*, 2143.

77. A. Togni; *Tetrahedron: Asymmetry*, **1991**, *2*, 683.

78. U. Burckhardt, M. Baumann, G. Trabesinger, V. Gramlich and A. Togni; *Organometallics*, **1997**, *16*, 5252.

79. Y. Uosumi, H. Danjo and T. Hayashi; *Tetrahedron Lett.*, **1997**, *38*, 3557.

80. J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin and J. M. J. Williams; *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2065.

81. J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter and L. Zsolnai; *Tetrahedron Lett.*, **1994**, *35*, 1523; H. Steinhagen, M. Reggelin and G. Helmchen; *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2108.

82. P. Von Matt and A. Pfaltz; *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 566; J. M. J. Williams; *Synlett*, **1996**, 705; H. Rieck and G. Helmchen; *Angew Chem. Int. Ed. Engl.*, **1995**, *34*, 2687; P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz and C. Lefeber, T. Feucht and G. Helmchen; *Tetrahedron: Asymmetry*, **1994**, *5*, 573.

83. B. Wiese and G. Helmchen; *Tetrahedron Lett.*, **1998**, *39*, 5727.

84. J. F. Bower, R. Jumnah, A. C. Williams and J. M. J. Williams; *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1411.

85. P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz and C. Lefeber, T. Feucht and G. Helmchen; *Tetrahedron: Asymmetry*, **1994**, *5*, 573.

86. B. M. Trost and P. E. Strege; *J. Am. Chem. Soc.*, **1977**, *99*, 1649.

87. J. S. Debenham, R. Madsen, C. Roberts and B. Fraser-Reid; *J. Am. Chem. Soc.*, **1995**, *117*, 3302; J. S. Debenham, S. D. Debenham and B. Fraser-Reid; *Bioorg. Med. Chem. Lett.*, **1996**, *4*, 1909; J. S. Debenham and B. Fraser-Reid; *J. Org. Chem.*, **1996**, *61*, 432.

88. R. Jumnah, PhD Thesis, Loughborough University, 1996.

89. E. P. Kohler, H. M. Chadwell; *Org. Synth.*, **1922**, *2*, 1; S. Ducki, R. Forrest, J. A. Hadfield, A. Kendall, N. J. Lawrence, A. T. McGowen and D. Rennison; *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1051.

90. A. L. Gemal and J-L. Luche; *J. Am. Chem. Soc.*, **1981**, *103*, 5454.

91. R. Spolton, PhD Thesis, University of Bath, 2000.

92. C. Girard and H. B. Kagan; *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 2922.

93. M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez and J. C. Palacios; *Tetrahedron: Asymmetry*, **1997**, *8*, 2997; D. G. Blackmond; *J. Am. Chem. Soc.*, **1997**, *119*, 12934.

94. C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami and H. B. Kagan; *J. Am. Chem. Soc.*, **1986**, *108*, 2353; K. Katsuki, K. B. Sharpless; *J. Am. Chem. Soc.*, **1980**, *102*, 5974; M. G. Finn, K. B. Sharpless; *J. Am. Chem. Soc.*, **1991**, *113*, 113.

95. M. Kitamura, S. Okada, R. Noyori; *J. Am. Chem. Soc.*, **1989**, *111*, 4028; M. Yamakawa, R. Noyori; *J. Am. Chem. Soc.*, **1995**, *117*, 6327.

96. A. J. Blacker, M. L. Clarke, M. S. Loft and J. M. J. Williams; *J. Chem. Soc., Chem. Commun.*, **1999**, 913.

97. Q. L. Zhou and A. Pfaltz; *Tetrahedron*, **1994**, *50*, 4467.

98. G. van Koten; *Pure Appl. Chem.*, **1994**, *66*, 1455.

99. K. L. Bray, C. P. Butts, M. Martin and G. C. Lloyd-Jones; *J. Chem. Soc., Dalton Commun.*, **1998**, 1421.

100. J. J. Mencel, J. R. Regan, J. Barton, P. R. Menard, J. G. Bruno, R. R. Calvo, B. E. Kornberg, A. Schwab, E. S. Neiss and J. T. Suh; *J. Med. Chem.*, **1990**, *33*, 1606; C. Bennion, R. C. Brown, A. R. Cook, C. N. Manners, D. W. Payling and D. H. Robinson; *J. Med. Chem.*, **1991**, *34*, 439; H. Urbach and R. Henning; *Tetrahedron Lett.*, **1984**, *25*, 1143; M. M. Campbell, B. C. Ross and G. Semple; *Tetrahedron Lett.*, **1989**, *30*, 1997.

101. C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil, C. A. Stone and A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann; *Nature*, **1980**, *288*, 280.

102. E. Bermejo Gonzalez, E. Farkas, A. A. Soudi, T. Tan, A. Yanovsky and K. B. Nolan; *J. Chem. Soc., Dalton Trans.*, **1997**, 2377.

103. M. E. Humphries, B. P. Clark and J. M. J. Williams; *Tetrahedron: Asymmetry*, **1998**, *9*, 749.

104. B. M. Trost, T. L. Calkins, C. Oertelt and J. Zambrano; *Tetrahedron Lett.*, **1998**, *39*, 1713.

105. J. M. J. Williams; *Synlett*, **1996**, 705.

106. T. Knöpfel, R. Kuhn and H. Allgeier; *J. Med. Chem.*, **1995**, *38*, 1417.

107. K. Shimamoto and Y. Ohfune; *J. Med. Chem.*, **1996**, *39*, 407.

108. I. Collado, J. Ezquerra, A. Mazón, C. Pedregal, B. Yruretagoyena, A. E. Kingston, R. Tomlinson, R. A. Wright, B. G. Johnson and D. D. Schoepp; *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 2849; K. Shimamoto and Y. Ohfune; *J. Med. Chem.*, **1996**, *39*, 407; N. Kurokawa and Y. Ohfune; *Tetrahedron Lett.*, **1985**, *26*, 83; A. S. Demir, C. Tanyeli, A. Cagir, M. N. Tahir and D. Ulku; *Tetrahedron: Asymmetry*, **1998**, *9*, 1035; P. Dauban, A. Chiaroni, C. Riche and R. H. Dodd; *J. Org. Chem*, **1996**, *61*, 2488; R. Pellicciari, B. Natalini and M. Marinozzi and J. B. Monahan, J. P. Snyder; *Tetrahedron Lett.*, **1990**, *31*, 139.

109. S. E. Denmark and J. P. Edwards; *J. Org. Chem.*, **1991**, *56*, 6974.

110. D. B. Miller; *Tetrahedron Lett.*, **1964**, 989.

111. K. Maruoka, Y. Fukutani and H. Yamamoto; *J. Org. Chem.*, **1985**, *50*, 4412.

112. P. Müller, C. Baud, D. Ené, S. Motallebi and M. P. Doyle, B. D. Brandes, A. B. Dyatkin, M. M. See; *Helv. Chim. Acta.*, **1995**, *78*, 459.

113. M. W. Majchrzak and A. Kotelko; *Synthesis*, **1983**, 470.

114. M. Suda; *Synthesis*, **1981**, 714.

115. G. A. Molander and L. S. Harring; *J. Org. Chem.*, **1989**, *54*, 3525.

116. G. Veeresa and A. Datta; *Tetrahedron Lett.*, **1998**, *39*, 3069; T. Gefflaut, U. Bauer, K. Airola and A. M. P. Koshinen; *Tetrahedron: Asymmetry,* **1996**, *7*, 3099; P. Dauban, A. Chiaroni, C. Riche and R. H. Dodd; *J. Org. Chem.*, **1996**, *61*, 2488; D. L. Boger and G. Schüle; *J. Org. Chem.*, **1998**, *63*, 6421; G. Casiraghi, G. Rassu, P. Spanu and L. Pinna; *Tetrahedron Lett.*, **1994**, *35*, 2423; S. Ho Kang and H. Choi; *J. Chem. Soc., Chem. Commun.*, **1996**, 1521; H. Sugimura, M. Miura and N. Yamada;

Tetrahedron: Asymmetry, **1997**, *8*, 4089; A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero; *Synthesis*, **1994**, 1450.

117. N. Chida, K. Koizumi, Y. Kitada, C. Yokoyama and S. Ogawa; *J. Chem. Soc., Chem. Commun.*, **1994**, 111.
118. R. Jumnah, PhD Thesis, Loughborough University, 1996.
119. P. Kocovský and I. Starý; *J. Org. Chem.*, **1990**, *55*, 3236.
120. H. Kogen and T. Nishi; *J. Chem. Soc., Chem. Commun.*, **1987**, 311.
121. A. Jenmalm, W. Berts, K. Luthman, I. Csöregh and U. Hacksell; *J. Org. Chem.*, **1995**, *60*, 1026.
122. A. Albeck and R. Persky; *J. Org. Chem.*, **1994**, *59*, 653.
123. Larock *Comprehensive Organic transformations*; VCH: New York, 1989, page 505-508.
124. D.P.G. Hamon, R.A. Massey-Westropp, J.L. Newton, *Tetrahedron: Asymmetry,* **1993**, *4*, 1435.
125. K. Soai, A. Ookawa, H. Oyamada and M. Takase; *Heterocycles,* **1982**, *19*, 1371.
126. R. O. Hutchins, I. M. Taffer and W. Burgoyne; *J. Org. Chem.*, **1981**, *46*, 5214.
127. E. Bartmann; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 653.
128. C. K. Bradsher and D. A. Hunt; *J. Org. Chem.*, **1981**, *46*, 4608.
129. Y. Kondo, T. Matsudaira, J. Sato, N. Murata and T. Sakamoto; *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 736; J. M. Chong, D. R. Cyr and E. K. Mar; *Tetrahedron Lett.*, **1987**, *28*, 5009; B. H. Lipshutz, J. Kozlowski and R. S. Wilhelm; *J. Am. Chem. Soc.*, **1982**, *104*, 2305.
130. B. H. Lipshutz, D. A. Parker, J. A. Kozlowski and S. L. Nguyen; *Tetrahedron Lett.*, **1984**, *25*, 5959.
131. B. H. Lipshutz, S. Whitney, J. A. Kozlowski and C. M. Breneman; *Tetrahedron Lett.*, **1986**, *27*, 4273; S. H. Bertz, C. P. Gibson and G. Dabbagh; *Tetrahedron Lett.*, **1987**, *28*, 4251.
132. P. G. Sammes and D. Thetford; *Tetrahedron Lett.*, **1986**, *27*, 2275.
133. C. Djerassi and R. R. Engle; *J. Am. Chem. Soc.*, **1953**, *75*, 3838.
134. S. Wolfe, S. K. Hasan, J. R. Campbell; *J. Chem. Soc., Chem. Commun.*, **1970**, 1420; H. Gopal and A. J. Gordon; *Tetrahedron Lett.*, **1971**, 2941.

135. Y. Yamamoto, H. Suzuki and Y. Moro-oka; *Tetrahedron Lett.*, **1985**, *26*, 2107; L. M. Berkowitz and P. N. Rylander; *J. Am. Chem. Soc.*, **1958**, *80*, 6682.

136. M. T. Nuñez and V. S. Martín; *J. Org. Chem.*, **1990**, *55*, 1928.

137. P. H. Carlsen, T. Katsuki, V. S. Martín and K. B. Sharpless; *J. Org. Chem.*, **1981**, *46*, 3936.

138. M. Matsumoto and N. Watanabe; *J. Org. Chem.*, **1984**, *49*, 3435; K. Kaneda, S. Haruna, T. Imanaka and K. Kawamoto; *J. Chem. Soc., Chem. Commun.*, **1990**, 1467.

139. S. Giddings and A.Mills; *J. Org. Chem.*, **1988**, *53*, 1103.

140. M. Schröder, W. P. Griffith; *J. Chem. Soc., Chem. Commun.*, **1979**, 58; L. A. Paquette, J. Dressel, P. D. Pansegran; *Tetrahedron Lett.*, **1987**, *28*, 4965; R. S. Varma and M. E. Hogan; *Tetrahedron Lett.*, **1992**, *33*, 7719.

141. M. Kasai and H. Ziffer; *J. Org. Chem.*, **1983**, *48*, 712.

142. J. M. Chong and K. B. Sharpless; *J. Org. Chem.*, **1985**, *50*, 1560.

143. R. M. Moriarty, H. Gopal and T. Adams; *Tetrahedron Lett.*, **1970**, 4003.

144. D. Askin, C. Angst and S. Danishefsky; *J. Org. Chem.*, **1987**, *52*, 622.

145. R. Hernández, D. Melián and E. Suárez; *Synthesis*, **1992**, 653.

146. Y. Gao and K. B. Sharpless; *J. Am. Chem. Soc.*, **1988**, *110*, 7538.

147. F. P. Schuda, M. B. Cichowicz, M. R. Heimann; *Tetrahedron Lett.*, **1983**, *24*, 3829.

148. R. Tang, S. E. Diamond, N. Neary and F. Mares; *J. Chem. Soc., Chem. Commun.*, **1978**, 562.

149. J. C. Sheeham and R. W. Tulis; *J. Org. Chem.*, **1974**, *39*, 2264.

150. B. E. Rossiter, T. Katsuki and K. B. Sharpless; *J. Am. Chem. Soc.*, **1981**, *103*, 464.

151. V. S. Martín, M. T. Nuñez and C. E. Tonn; *Tetrahedron Lett.*, **1988**, *29*, 2701.

152. A. K. Chakraborti and U. Ranjan Ghatak; *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2605.

153. M. J. Sloan and K. L. Kirk; *Tetrahedron Lett.*, **1997**, *38*, 1677.

154. S. Ghosh and U. Ranjan Ghatak; *Tetrahedron*, **1992**, *48*, 7289; K. C. Hansen, Q. Lin and T. M. Aminabhavi; *J. Chem. Soc., Faraday Trans.*, **1996**, *92*, 3643.

155. P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello; *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2469.
156. T. Honda and N. Kimura; *J. Chem. Soc., Chem. Commun.*, **1994**, 77.
157. F. Matsuura, Y. Hamada and T. Shioiri; *Tetrahedron*, **1993**, *49*, 8211.
158. R. Giovannini and M. Petrini; *Tetrahedron Lett.*, **1997**, *38*, 3781.
159. F. Matsuura, Y. Hamada and T. Shioiri; *Tetrahedron Lett.*, **1994**, *35*, 733.
160. E. J. Corey and P. B. Hopkins; *Tetrahedron Lett.*, **1982**, *23*, 4871.
161. A. Dondondi, F. Junquera, F. L. Merchan, P. Merino and T. Tejero; *Synthesis*, **1994**, 1450; A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan and A. K. Ganguly; *J. Org. Chem.*, **1986**, *51*, 5024; B. K. Banik, M. S. Manhas and A. K. Bose; *J. Org. Chem.*, **1993**, *58*, 307; G. Casiraghi, G. Rassu, P. Spanu and L. Pinna; *Tetrahedron Lett.*, **1994**, *35*, 2423.
162. F. Toda, S. Soda and I. Goldberg; *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2357.
163. D. R. Mootoo and B. Fraser-Reid; *J. Chem. Soc., Perkin Trans. 1*, **1990**, 739; Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka and O. Yonemitsu; *Tetrahedron Lett.*, **1984**, *25*, 5393; A. Fürstner and I. Konetzki; *J. Org. Chem.*, **1998**, *63*, 3072.
164. C. Y. Chen, S. Nagumo and H. Akita; *Chem. Pharm. Bull.*, **1996**, 2153.
165. H. Klein and A. Steinmetz; *Tetrahedron Lett.*, **1975**, *48*, 4249.
166. J. A. Marshall, A. W. Garofalo and R. C. Sedrani; *Synlett*, **1992**, 643.
167. J. V. Allen, G. J. Dawson, C. G. Frost and J. M. J. Williams; *Tetrahedron*, **1994**, 799.

Appendix A

Supplementary data on Figure 2.1 (the X-ray crystal structure for compound (ent-30a)).

A crystal of approximate dimensions 0.23 x 0.30 x 0.30 mm was used for data collection.

Crystal data: $C_{24}H_{24}NOP$, M = 373.41, Orthorhombic , a = 8.702(2), b = 13.980(2), c = 17.329(2) Å , = 90, = 103.16(2), = 90°, U = 2052.8(6) Å^3, space group $P2_1$, Z = 4, D_c = 1.208 gcm^{-3}, (M o -K) = 0.147 mm^{-1}, F(000) = 792. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.40< <24.97°. Data (4109 reflections) were corrected for Lorentz and polarization and also for extinction.

The asymmetric unit was seento consist of 2 molecules of similar chirality. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 2973 F^2 data with Fo>4(Fo)] $R1$ = 0.0345 and $wR2$ = 0.0871. Goodness of fit = 0.976. The max. and min. residual densities were 0.217 and -0.152 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.
2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.

3. McArdle P., J.Appl.Cryst., 28, 65, 1995

Table 1. Crystal data and structure refinement for **(ent-30a)**.

Identification code	99jmjw1/m.humphries
Empirical formula	$C_{24}H_{24}NOP$
Formula weight	373.41
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	$P2_1$
Unit cell dimensions	a = 8.702(2)Å
	b = 13.980(2)Å
	c = 17.329(2)Å
Volume	2052.8(6) $Å^3$
Z	4
Density (calculated)	1.208 Mg/m^3
Absorption coefficient	0.147 mm^{-1}
F(000)	792
Crystal size	0.23 x 0.30 x 0.30 mm
Theta range for data collection	2.40 to 24.97 °.
Index ranges	0<=h<=9; 0<=k<=16; -19<=l<=19
Reflections collected	4109
Independent reflections	3715 [R(int) = 0.0128]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3709 / 1 / 492
Goodness-of-fit on F^2	0.976
Final R indices [I>2 (I)]	R1 = 0.0345 wR2 = 0.0871
R indices (all data)	R1 = 0.0473 wR2 = 0.0922
Absolute structure parameter	0.00
Largest diff. peak and hole	0.217 and -0.152 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\ ^2(Fo^2)+(0.0581P)^2+0.1509P]$ where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0034(8)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\ ^3/\sin(2\ )]^{-1/4}$

able 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **(ent-30a)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
P(1)	2119(1)	7248(1)	3566(1)	46(1)
O(2)	-767(4)	4908(3)	4216(2)	76(1)
N(2)	1099(4)	5306(3)	3560(2)	56(1)
C(1)	1890(4)	7184(3)	2483(2)	48(1)
C(2)	3090(5)	6746(3)	2203(2)	59(1)

C(3)	3047(6)	6733(4)	1394(3)	70(2)
C(4)	1812(7)	7139(4)	865(3)	73(2)
C(5)	605(7)	7560(4)	1127(3)	72(2)
C(6)	643(5)	7580(4)	1935(2)	61(1)
C(7)	2797(4)	8490(3)	3761(2)	48(1)
C(8)	3199(5)	9116(4)	3215(3)	63(1)
C(9)	3907(6)	9978(4)	3455(3)	74(1)
C(10)	4185(5)	10259(4)	4230(3)	75(1)
C(11)	3774(6)	9669(4)	4772(3)	73(1)
C(12)	3105(5)	8786(4)	4548(3)	64(1)
C(13)	34(4)	7343(3)	3636(2)	45(1)
C(14)	-707(5)	8217(4)	3639(3)	56(1)
C(15)	-2245(6)	8288(4)	3731(3)	69(2)
C(16)	-3067(5)	7490(4)	3829(3)	73(1)
C(17)	-2373(5)	6600(5)	3832(3)	73(2)
C(18)	-837(5)	6513(4)	3737(2)	51(1)
C(19)	-106(5)	5554(3)	3804(2)	51(1)
C(20)	85(6)	4021(4)	4151(3)	79(2)
C(21)	1565(5)	4351(3)	3902(2)	56(1)
C(22)	2150(5)	3667(3)	3357(2)	68(1)
C(23)	2728(7)	2749(4)	3799(3)	96(2)
C(24)	3410(7)	4082(4)	3009(3)	92(2)
P(2)	2036(1)	6366(1)	8549(1)	45(1)
O(1)	-1057(4)	8677(3)	9088(2)	79(1)
N(1)	714(4)	8281(3)	8386(2)	54(1)
C(25)	1818(4)	6419(3)	7471(2)	46(1)
C(26)	570(5)	5998(3)	6927(2)	59(1)
C(27)	533(6)	6010(4)	6127(3)	65(1)
C(28)	1725(6)	6439(4)	5855(3)	66(1)
C(29)	2937(6)	6867(4)	6390(3)	67(1)
C(30)	2996(4)	6851(3)	7190(2)	55(1)
C(31)	2768(4)	5134(3)	8765(2)	45(1)
C(32)	3070(5)	4846(4)	9548(2)	60(1)
C(33)	3720(5)	3965(4)	9781(3)	73(1)
C(34)	4106(5)	3353(4)	9226(3)	76(1)
C(35)	3836(6)	3634(4)	8448(3)	80(2)
C(36)	3171(5)	4529(3)	8221(3)	62(1)
C(37)	-28(5)	6228(3)	8643(2)	48(1)
C(38)	-708(5)	5321(4)	8661(3)	58(1)
C(39)	-2211(5)	5209(4)	8783(3)	64(1)
C(40)	-3087(6)	5996(4)	8887(3)	74(2)
C(41)	-2453(5)	6898(4)	8864(3)	65(1)
C(42)	-925(5)	7028(3)	8748(2)	51(1)
C(43)	-335(5)	7998(4)	8718(3)	52(1)
C(44)	-231(6)	9550(4)	9043(3)	81(2)
C(45)	853(4)	9334(3)	8487(2)	57(1)
C(46)	2542(5)	9663(3)	8777(3)	64(1)
C(47)	3564(7)	9343(5)	8218(4)	106(2)
C(48)	2627(7)	10748(4)	8899(4)	96(2)

Table 3. Bond lengths [Å] and angles [°] for **(ent-30a)**.

P(1)-C(1)	1.843(4)
P(1)-C(7)	1.840(5)
P(1)-C(13)	1.851(4)
O(2)-C(19)	1.358(5)
O(2)-C(20)	1.462(6)
N(2)-C(19)	1.265(5)
N(2)-C(21)	1.479(5)
C(1)-C(6)	1.384(5)
C(1)-C(2)	1.390(5)
C(2)-C(3)	1.393(6)
C(3)-C(4)	1.367(7)
C(4)-C(5)	1.369(8)
C(5)-C(6)	1.393(6)
C(7)-C(8)	1.391(6)
C(7)-C(12)	1.391(5)
C(8)-C(9)	1.374(7)
C(9)-C(10)	1.366(6)
C(10)-C(11)	1.358(7)
C(11)-C(12)	1.382(7)
C(13)-C(14)	1.382(7)
C(13)-C(18)	1.418(6)
C(14)-C(15)	1.387(6)
C(15)-C(16)	1.358(7)
C(16)-C(17)	1.382(8)
C(17)-C(18)	1.389(6)
C(18)-C(19)	1.477(7)
C(20)-C(21)	1.520(6)
C(21)-C(22)	1.511(5)
C(22)-C(24)	1.484(7)
C(22)-C(23)	1.521(6)
P(2)-C(25)	1.836(4)
P(2)-C(31)	1.845(4)
P(2)-C(37)	1.850(4)
O(1)-C(43)	1.376(5)
O(1)-C(44)	1.427(6)
N(1)-C(43)	1.249(5)
N(1)-C(45)	1.485(5)
C(25)-C(30)	1.370(5)
C(25)-C(26)	1.395(5)
C(26)-C(27)	1.379(6)
C(27)-C(28)	1.371(7)
C(28)-C(29)	1.373(7)
C(29)-C(30)	1.376(6)
C(31)-C(36)	1.371(6)
C(31)-C(32)	1.382(5)
C(32)-C(33)	1.376(7)
C(33)-C(34)	1.385(7)
C(34)-C(35)	1.371(6)
C(35)-C(36)	1.396(7)
C(37)-C(38)	1.403(7)
C(37)-C(42)	1.399(6)

C(38)-C(39)	1.380(6)
C(39)-C(40)	1.373(7)
C(40)-C(41)	1.380(7)
C(41)-C(42)	1.401(6)
C(42)-C(43)	1.455(7)
C(44)-C(45)	1.523(6)
C(45)-C(46)	1.512(5)
C(46)-C(47)	1.523(7)
C(46)-C(48)	1.531(7)
C(1)-P(1)-C(7)	100.9(2)
C(1)-P(1)-C(13)	101.0(2)
C(7)-P(1)-C(13)	101.4(2)
C(19)-O(2)-C(20)	103.9(3)
C(19)-N(2)-C(21)	106.6(4)
C(6)-C(1)-C(2)	118.1(3)
C(6)-C(1)-P(1)	124.4(3)
C(2)-C(1)-P(1)	117.5(3)
C(3)-C(2)-C(1)	120.4(4)
C(2)-C(3)-C(4)	120.4(5)
C(5)-C(4)-C(3)	120.1(4)
C(4)-C(5)-C(6)	119.9(5)
C(1)-C(6)-C(5)	121.1(4)
C(8)-C(7)-C(12)	117.2(4)
C(8)-C(7)-P(1)	126.0(3)
C(12)-C(7)-P(1)	116.3(3)
C(9)-C(8)-C(7)	120.7(5)
C(10)-C(9)-C(8)	121.1(5)
C(9)-C(10)-C(11)	119.3(5)
C(10)-C(11)-C(12)	120.6(5)
C(11)-C(12)-C(7)	121.1(5)
C(14)-C(13)-C(18)	117.4(4)
C(14)-C(13)-P(1)	121.9(3)
C(18)-C(13)-P(1)	120.6(3)
C(13)-C(14)-C(15)	121.8(5)
C(16)-C(15)-C(14)	120.4(5)
C(15)-C(16)-C(17)	119.9(4)
C(16)-C(17)-C(18)	120.7(5)
C(17)-C(18)-C(13)	119.9(5)
C(17)-C(18)-C(19)	118.6(5)
C(13)-C(18)-C(19)	121.3(4)
N(2)-C(19)-O(2)	118.4(4)
N(2)-C(19)-C(18)	126.7(4)
O(2)-C(19)-C(18)	114.7(4)
O(2)-C(20)-C(21)	104.0(4)
N(2)-C(21)-C(20)	102.4(3)
N(2)-C(21)-C(22)	114.9(3)
C(20)-C(21)-C(22)	114.4(4)
C(24)-C(22)-C(21)	113.0(4)
C(24)-C(22)-C(23)	110.2(4)
C(21)-C(22)-C(23)	109.8(4)
C(25)-P(2)-C(31)	101.2(2)
C(25)-P(2)-C(37)	102.5(2)

C(31)-P(2)-C(37)	100.5(2)
C(43)-O(1)-C(44)	106.0(3)
C(43)-N(1)-C(45)	107.9(4)
C(30)-C(25)-C(26)	118.4(3)
C(30)-C(25)-P(2)	117.8(3)
C(26)-C(25)-P(2)	123.6(3)
C(27)-C(26)-C(25)	120.7(4)
C(26)-C(27)-C(28)	120.3(4)
C(29)-C(28)-C(27)	118.9(4)
C(28)-C(29)-C(30)	121.3(5)
C(25)-C(30)-C(29)	120.4(4)
C(36)-C(31)-C(32)	118.3(4)
C(36)-C(31)-P(2)	124.6(3)
C(32)-C(31)-P(2)	116.8(3)
C(33)-C(32)-C(31)	121.5(5)
C(32)-C(33)-C(34)	119.8(5)
C(33)-C(34)-C(35)	119.4(5)
C(34)-C(35)-C(36)	120.1(5)
C(31)-C(36)-C(35)	120.9(5)
C(38)-C(37)-C(42)	118.0(4)
C(38)-C(37)-P(2)	121.3(3)
C(42)-C(37)-P(2)	120.7(3)
C(39)-C(38)-C(37)	121.7(5)
C(40)-C(39)-C(38)	120.2(5)
C(39)-C(40)-C(41)	119.4(4)
C(42)-C(41)-C(40)	121.4(5)
C(41)-C(42)-C(37)	119.4(4)
C(41)-C(42)-C(43)	118.7(4)
C(37)-C(42)-C(43)	121.9(4)
N(1)-C(43)-O(1)	117.1(4)
N(1)-C(43)-C(42)	127.8(4)
O(1)-C(43)-C(42)	115.1(4)
O(1)-C(44)-C(45)	104.9(4)
N(1)-C(45)-C(46)	112.8(3)
N(1)-C(45)-C(44)	103.1(3)
C(46)-C(45)-C(44)	115.1(3)
C(45)-C(46)-C(47)	111.4(4)
C(45)-C(46)-C(48)	111.1(4)
C(47)-C(46)-C(48)	111.2(5)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(ent-30a)**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
P(1)	43(1)	44(1)	53(1)	4(1)	14(1)	4(1)
O(2)	78(2)	73(2)	90(2)	26(2)	43(2)	-3(2)
N(2)	58(2)	48(2)	65(2)	4(2)	20(2)	-2(2)
C(1)	46(2)	42(2)	57(2)	0(2)	14(2)	-5(2)

C(2)	55(2)	50(3)	77(3)	-2(2)	28(2)	1(2)
C(3)	76(3)	72(3)	74(3)	-20(3)	41(3)	-6(3)
C(4)	97(4)	75(4)	52(3)	-10(3)	25(3)	-15(3)
C(5)	85(3)	81(4)	49(3)	4(3)	13(3)	4(3)
C(6)	56(2)	68(3)	63(3)	-2(2)	21(2)	5(2)
C(7)	43(2)	50(3)	52(2)	1(2)	11(2)	4(2)
C(8)	71(3)	62(3)	56(2)	13(2)	15(2)	-8(2)
C(9)	83(3)	50(3)	90(4)	5(3)	25(3)	-18(3)
C(10)	77(3)	50(3)	95(4)	-8(3)	14(3)	-4(3)
C(11)	89(3)	65(3)	67(3)	-19(3)	23(3)	0(3)
C(12)	74(3)	59(3)	63(3)	-1(3)	24(2)	1(3)
C(13)	43(2)	52(2)	43(2)	4(2)	13(2)	6(2)
C(14)	49(3)	57(3)	62(3)	7(2)	14(2)	7(2)
C(15)	61(3)	84(4)	63(3)	3(3)	16(2)	28(3)
C(16)	44(2)	102(4)	77(3)	5(3)	23(2)	4(3)
C(17)	51(3)	94(4)	77(3)	17(3)	21(2)	2(3)
C(18)	49(2)	64(3)	43(2)	1(2)	14(2)	-5(2)
C(19)	56(2)	49(2)	49(2)	2(2)	11(2)	-4(2)
C(20)	84(3)	63(3)	91(3)	27(3)	24(3)	5(3)
C(21)	59(2)	51(2)	54(2)	7(2)	5(2)	-5(2)
C(22)	77(3)	58(2)	60(2)	-1(2)	0(2)	6(2)
C(23)	100(4)	59(3)	127(5)	21(3)	19(4)	11(3)
C(24)	113(4)	71(3)	106(4)	9(3)	56(3)	14(3)
P(2)	42(1)	46(1)	48(1)	-7(1)	13(1)	-4(1)
O(1)	68(2)	63(2)	117(2)	-19(2)	42(2)	7(2)
N(1)	62(2)	50(2)	52(2)	-5(2)	19(2)	0(2)
C(25)	47(2)	45(2)	50(2)	-1(2)	19(2)	1(2)
C(26)	57(2)	66(3)	52(2)	-5(2)	10(2)	-12(2)
C(27)	63(3)	70(4)	57(3)	-2(2)	7(2)	6(3)
C(28)	81(3)	68(3)	53(3)	6(3)	24(2)	13(3)
C(29)	68(3)	73(3)	69(3)	6(3)	36(3)	0(2)
C(30)	53(2)	59(3)	54(2)	-2(2)	16(2)	-2(2)
C(31)	35(2)	43(2)	60(2)	-8(2)	15(2)	-4(2)
C(32)	65(2)	61(3)	56(2)	3(2)	21(2)	6(2)
C(33)	68(3)	72(4)	79(3)	18(3)	16(2)	-1(3)
C(34)	68(3)	57(3)	104(4)	12(3)	20(3)	10(3)
C(35)	93(4)	68(4)	80(3)	-13(3)	21(3)	12(3)
C(36)	66(3)	56(3)	64(3)	-1(2)	13(2)	6(2)
C(37)	43(2)	60(3)	43(2)	-9(2)	12(2)	-2(2)
C(38)	57(3)	56(3)	65(3)	-4(2)	23(2)	-10(2)
C(39)	53(3)	69(3)	71(3)	-5(2)	17(2)	-18(2)
C(40)	49(2)	101(4)	77(3)	-15(3)	25(2)	-21(3)
C(41)	49(3)	76(3)	75(3)	-12(3)	23(2)	8(2)
C(42)	44(2)	61(3)	50(2)	-8(2)	15(2)	-4(2)
C(43)	45(2)	65(3)	47(2)	-12(2)	11(2)	14(2)
C(44)	71(3)	59(3)	117(4)	-22(3)	34(3)	4(2)
C(45)	58(2)	52(2)	59(2)	-3(2)	6(2)	5(2)
C(46)	69(2)	58(2)	68(3)	-7(2)	19(2)	-3(2)
C(47)	104(4)	95(4)	132(5)	-26(4)	57(3)	-17(3)
C(48)	97(4)	70(4)	128(5)	-25(3)	37(4)	-18(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(ent-30a)**.

Atom	x	y	z	U(eq)
H(2)	3928(5)	6460(3)	2557(2)	70
H(3)	3864(6)	6447(4)	1213(3)	84
H(4)	1791(7)	7128(4)	326(3)	88
H(5)	-238(7)	7833(4)	767(3)	87
H(6)	-184(5)	7864(4)	2109(2)	73
H(8)	2986(5)	8949(4)	2681(3)	76
H(9)	4203(6)	10376(4)	3085(3)	88
H(10)	4651(5)	10848(4)	4384(3)	89
H(11)	3945(6)	9860(4)	5298(3)	87
H(12)	2856(5)	8384(4)	4929(3)	77
H(14)	-159(5)	8773(4)	3578(3)	67
H(15)	-2715(6)	8886(4)	3725(3)	83
H(16)	-4095(5)	7541(4)	3895(3)	87
H(17)	-2941(5)	6055(5)	3898(3)	88
H(20A)	-539(6)	3600(4)	3755(3)	94
H(20B)	350(6)	3688(4)	4655(3)	94
H(21)	2404(5)	4436(3)	4381(2)	67
H(22)	1256(5)	3505(3)	2921(2)	81
H(23A)	3641(26)	2883(6)	4213(14)	145
H(23B)	2998(40)	2293(10)	3437(5)	145
H(23C)	1908(17)	2490(14)	4026(18)	145
H(24A)	3704(31)	3629(11)	2653(17)	137
H(24B)	4312(18)	4230(25)	3425(4)	137
H(24C)	3028(17)	4656(15)	2725(19)	137
H(26)	-244(5)	5706(3)	7106(2)	70
H(27)	-304(6)	5726(4)	5771(3)	77
H(28)	1712(6)	6440(4)	5317(3)	79
H(29)	3734(6)	7174(4)	6208(3)	80
H(30)	3840(4)	7134(3)	7542(2)	65
H(32)	2828(5)	5256(4)	9926(2)	72
H(33)	3899(5)	3782(4)	10310(3)	88
H(34)	4543(5)	2756(4)	9379(3)	91
H(35)	4096(6)	3229(4)	8072(3)	96
H(36)	2999(5)	4716(3)	7693(3)	74
H(38)	-131(5)	4781(4)	8590(3)	70
H(39)	-2631(5)	4599(4)	8795(3)	76
H(40)	-4098(6)	5922(4)	8972(3)	89
H(41)	-3052(5)	7430(4)	8928(3)	78
H(44A)	377(6)	9737(4)	9562(3)	97
H(44B)	-961(6)	10061(4)	8832(3)	97
H(45)	414(4)	9638(3)	7975(2)	69
H(46)	2961(5)	9361(3)	9292(3)	77
H(47A)	3135(29)	9591(25)	7697(7)	158
H(47B)	3583(39)	8657(5)	8198(19)	158
H(47C)	4619(15)	9580(26)	8408(14)	158

H(48A)	2355(43)	11062(4)	8394(4)	145
H(48B)	3680(13)	10924(5)	9168(20)	145
H(48C)	1901(32)	10936(5)	9213(19)	145

Appendix B

Supplementary data on Figure 4.1 (the X-ray crystal structure for compound (120)).

A crystal of approximate dimensions 0.3 x 0.4 x 0.2 mm was used for data collection.

Crystal data: $C_{24}H_{21}NO_2$, M = 355.42, Orthorhombic , a = 6.8240(10), b = 8.455(3), c = 34.404(12) Å, U = 1985.0(10) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.189 gcm^{-3}, (Mo-K) = 0.075 mm^{-1}, F(000) = 752. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.36< <22.92°. Data (1620 reflections) were corrected for Lorentz and polarization but not for absorption.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

Examination of the gross structure revealed the presence of a hydrogen-bonding feature along the a axis which results in lattice domination by 1-dimensional polymers in this direction. Typically, H2 as presented interacts with O1 in the asymmetric unit generated via the symmetry operation $1+x, y, z$. [H2...O1 1.98(7)Å, O2-H2-O1 151(14)°]

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 673 F^2 data with Fo>4 (Fo)] $R1$ = 0.0754 and $wR2$ = 0.1189. Goodness of fit = 1.067. The max. and min. residual densities were 0.206 and -0.238 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances

and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.
2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.
3. McArdle P., J.Appl.Cryst., 27, 438, 1994

Table 1. Crystal data and structure refinement for **(120)**.

Identification code	97jmjw3/m/humphries
Empirical formula	$C_{24}H_{21}NO_2$
Formula weight	355.42
Temperature	293(2)°K
Wavelength	0.70930 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.8240(10)Å
	b = 8.455(3)Å
	c = 34.404(12)Å
Volume	1985.0(10) $Å^3$
Z	4
Density (calculated)	1.189 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	752
Crystal size	0.3 x 0.4 x 0.2 mm
Theta range for data collection	2.36 to 22.92 °.
Index ranges	-7<=h<=0; 0<=k<=8; -37<=l<=0
Reflections collected	1620
Independent reflections	1620 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1595 / 0 / 247
Goodness-of-fit on F^2	1.067
Final R indices [I>2 (I)]	R1 = 0.0754 wR2 = 0.1189
R indices (all data)	R1 = 0.2087 wR2 = 0.2304
Absolute structure parameter	-8(8)
Largest diff. peak and hole	0.206 and -0.238 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\ ^2(Fo^2)+(0.0580P)^2+0.0000P]$

	where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0078(22)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\ ^3/\sin(2\ )]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (**120**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	-2883(12)	-8515(11)	-1440(3)	37(3)
O(1)	-5911(11)	-8632(11)	-1718(2)	51(3)
O(2)	392(11)	-7760(10)	-1504(3)	55(3)
C(1)	-4133(18)	-8893(14)	-1729(3)	40(3)
C(2)	-2949(17)	-9694(14)	-2031(3)	35(3)
C(3)	-3611(19)	-10183(18)	-2400(4)	60(4)
C(4)	-2197(24)	-10871(17)	-2634(4)	73(5)
C(5)	-282(25)	-11041(20)	-2513(5)	81(5)
C(6)	286(19)	-10473(15)	-2155(4)	54(4)
C(7)	-1069(16)	-9797(14)	-1911(3)	40(3)
C(8)	-850(15)	-9097(13)	-1509(4)	44(3)
C(9)	-230(19)	-10317(16)	-1216(3)	59(4)
C(10)	-3100(21)	-5070(16)	-1519(4)	59(4)
C(11)	-3731(23)	-3674(18)	-1656(4)	72(5)
C(12)	-5486(25)	-3031(18)	-1532(5)	82(5)
C(13)	-6557(27)	-3849(18)	-1269(6)	112(7)
C(14)	-5874(23)	-5300(18)	-1124(4)	75(5)
C(15)	-4167(17)	-5938(14)	-1244(3)	41(3)
C(16)	-3343(16)	-7501(14)	-1103(3)	40(3)
C(17)	-4590(19)	-8402(15)	-823(3)	51(4)
C(18)	-4175(19)	-8602(17)	-457(3)	50(3)
C(19)	-5313(20)	-9451(16)	-162(4)	54(4)
C(20)	-6935(21)	-10320(20)	-232(4)	73(5)
C(21)	-7952(28)	-11119(22)	53(5)	95(6)
C(22)	-7250(26)	-11138(21)	415(5)	79(5)
C(23)	-5636(29)	-10349(19)	509(4)	81(5)
C(24)	-4651(20)	-9512(20)	211(4)	68(4)

Table 3. Bond lengths [Å] and angles [°] for (**120**).

N(1)-C(1)	1.348(13)
N(1)-C(16)	1.477(13)
N(1)-C(8)	1.492(13)
O(1)-C(1)	1.234(13)
O(2)-C(8)	1.413(12)
C(1)-C(2)	1.48(2)
C(2)-C(7)	1.35(2)
C(2)-C(3)	1.41(2)
C(3)-C(4)	1.38(2)
C(4)-C(5)	1.38(2)
C(5)-C(6)	1.38(2)
C(6)-C(7)	1.37(2)
C(7)-C(8)	1.51(2)
C(8)-C(9)	1.50(2)
C(10)-C(11)	1.34(2)
C(10)-C(15)	1.40(2)
C(11)-C(12)	1.38(2)
C(12)-C(13)	1.35(2)
C(13)-C(14)	1.40(2)
C(14)-C(15)	1.35(2)
C(15)-C(16)	1.52(2)
C(16)-C(17)	1.49(2)
C(17)-C(18)	1.30(2)
C(18)-C(19)	1.46(2)
C(19)-C(20)	1.35(2)
C(19)-C(24)	1.36(2)
C(20)-C(21)	1.38(2)
C(21)-C(22)	1.34(2)
C(22)-C(23)	1.33(2)
C(23)-C(24)	1.42(2)
C(1)-N(1)-C(16)	125.6(10)
C(1)-N(1)-C(8)	113.1(10)
C(16)-N(1)-C(8)	121.0(9)
O(1)-C(1)-N(1)	123.8(12)
O(1)-C(1)-C(2)	129.9(11)
N(1)-C(1)-C(2)	106.3(10)
C(7)-C(2)-C(3)	124.1(11)
C(7)-C(2)-C(1)	109.5(9)
C(3)-C(2)-C(1)	126.2(11)
C(4)-C(3)-C(2)	115.0(12)
C(3)-C(4)-C(5)	121.9(14)
C(6)-C(5)-C(4)	120.1(14)
C(7)-C(6)-C(5)	120.1(13)
C(2)-C(7)-C(6)	118.7(10)
C(2)-C(7)-C(8)	110.4(9)

C(6)-C(7)-C(8)	130.9(11)
O(2)-C(8)-N(1)	107.0(8)
O(2)-C(8)-C(9)	111.8(10)
N(1)-C(8)-C(9)	112.4(10)
O(2)-C(8)-C(7)	112.6(10)
N(1)-C(8)-C(7)	100.5(9)
C(9)-C(8)-C(7)	111.9(9)
C(11)-C(10)-C(15)	122.0(14)
C(10)-C(11)-C(12)	121(2)
C(13)-C(12)-C(11)	118(2)
C(12)-C(13)-C(14)	120(2)
C(15)-C(14)-C(13)	122(2)
C(14)-C(15)-C(10)	116.5(13)
C(14)-C(15)-C(16)	124.8(12)
C(10)-C(15)-C(16)	118.7(11)
N(1)-C(16)-C(17)	109.3(10)
N(1)-C(16)-C(15)	109.5(8)
C(17)-C(16)-C(15)	116.1(10)
C(18)-C(17)-C(16)	124.5(12)
C(17)-C(18)-C(19)	128.2(12)
C(20)-C(19)-C(24)	114.8(12)
C(20)-C(19)-C(18)	125.3(13)
C(24)-C(19)-C(18)	119.6(12)
C(19)-C(20)-C(21)	123.5(14)
C(22)-C(21)-C(20)	119(2)
C(23)-C(22)-C(21)	121(2)
C(22)-C(23)-C(24)	118(2)
C(19)-C(24)-C(23)	122.9(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for (**120**). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^* 2 U11 + ... + 2 h k a^* b^* U12]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	17(5)	50(7)	44(6)	0(5)	6(5)	3(5)
O(1)	22(5)	67(7)	66(6)	-4(5)	-2(4)	6(5)
O(2)	26(5)	67(6)	72(6)	-13(5)	3(5)	1(5)
C(1)	36(7)	41(8)	42(8)	0(6)	-12(7)	-10(7)
C(2)	38(7)	46(7)	22(6)	-7(6)	2(5)	-9(7)
C(3)	48(8)	73(10)	59(9)	-2(8)	-7(7)	-12(8)
C(4)	83(11)	79(13)	56(9)	-35(8)	7(9)	3(11)
C(5)	65(10)	81(11)	95(11)	-40(10)	28(10)	-2(10)
C(6)	44(8)	52(8)	67(9)	-13(8)	10(8)	-2(8)
C(7)	35(7)	40(7)	47(7)	-14(6)	7(6)	-3(7)
C(8)	17(6)	39(8)	75(8)	-21(7)	-4(6)	5(6)
C(9)	46(8)	64(9)	66(9)	23(8)	-12(7)	14(8)
C(10)	70(9)	43(9)	64(8)	5(8)	12(8)	3(8)
C(11)	73(12)	45(10)	96(12)	4(9)	5(10)	-9(9)
C(12)	82(11)	52(10)	113(12)	28(10)	7(11)	15(10)
C(13)	96(13)	45(10)	195(19)	46(12)	71(14)	31(10)
C(14)	68(10)	66(10)	92(11)	9(9)	41(9)	25(10)
C(15)	38(7)	43(8)	41(7)	-8(6)	-5(6)	5(7)
C(16)	36(7)	53(9)	29(6)	4(6)	9(5)	-3(7)
C(17)	47(8)	51(9)	56(8)	6(7)	1(7)	5(7)
C(18)	46(7)	76(9)	29(6)	-1(7)	-5(6)	-5(8)
C(19)	55(9)	51(9)	56(9)	0(7)	13(8)	-4(8)
C(20)	65(10)	107(13)	47(8)	13(10)	-15(8)	-18(11)
C(21)	106(13)	122(16)	59(10)	1(10)	20(10)	-55(13)
C(22)	89(13)	86(13)	61(11)	25(9)	11(10)	-7(12)
C(23)	104(15)	73(12)	67(10)	-1(9)	-1(11)	8(12)
C(24)	51(8)	106(13)	48(8)	11(8)	9(7)	-11(10)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (**120**).

Atom	x	y	z	U(eq)
H(2)	1534(20)	-8048(12)	-1483(43)	82
H(3)	-4902(19)	-10054(18)	-2481(4)	72
H(4)	-2548(24)	-11228(17)	-2880(4)	87
H(5)	626(25)	-11540(20)	-2673(5)	97
H(6)	1590(19)	-10547(15)	-2078(4)	65
H(9A)	-1115(81)	-11199(50)	-1225(19)	88
H(9B)	-252(130)	-9860(35)	-961(5)	88
H(9C)	1073(55)	-10672(81)	-1275(16)	88
H(10)	-1917(21)	-5474(16)	-1610(4)	71
H(11)	-2975(23)	-3130(18)	-1836(4)	86
H(12)	-5918(25)	-2062(18)	-1627(5)	99
H(13)	-7752(27)	-3448(18)	-1185(6)	135
H(14)	-6619(23)	-5835(18)	-939(4)	90
H(16)	-2103(16)	-7270(14)	-971(3)	47
H(17)	-5741(19)	-8851(15)	-917(3)	61
H(18)	-3010(19)	-8149(17)	-371(3)	60
H(20)	-7390(21)	-10382(20)	-487(4)	87
H(21)	-9115(28)	-11640(22)	-7(5)	114
H(22)	-7904(26)	-11715(21)	605(5)	94
H(23)	-5168(29)	-10346(19)	763(4)	98
H(24)	-3499(20)	-8980(20)	273(4)	82

Appendix C

Supplementary data on Figure 4.2 (the X-ray crystal structure for compound (126)).

A crystal of approximate dimensions 0.4 x 0.4 x 0.3 mm was used for data collection.

Crystal data: $C_{23}H_{17}NO_3$, M = 355.38, Orthorhombic , a = 8.719(2), b = 11.315(2), c = 18.713(4) Å, U = 1846.1(7) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.279 gcm^{-3}, (Mo-K) = 0.085 mm^{-1}, F(000) = 744. Crystallographic measurements were made at 293(2)°K on a CAD4 automatic four-circle diffractometer in the range 2.10< <23.92°. Data (2187 reflections) were corrected for Lorentz and polarization and also for absorption.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 1225 F^2 data with Fo>4(Fo)] $R1$ = 0.0455 and $wR2$ = 0.1081. Goodness of fit = 0.908. The max. and min. residual densities were 0.174 and -0.138 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.
2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.

3. McArdle P., J.Appl.Cryst., 27, 438, 1994

Table 1. Crystal data and structure refinement for **126**.

Identification code	97jmjw2
Empirical formula	$C_{23} H_{17} N O_3$
Formula weight	355.38
Temperature	293(2)°K
Wavelength	0.70930 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.719(2)Å
	b = 11.315(2)Å
	c = 18.713(4)Å
Volume	1846.1(7) $Å^3$
Z	4
Density (calculated)	1.279 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	744
Crystal size	0.4 x 0.4 x 0.3 mm
Theta range for data collection	2.10 to 23.92 °.
Index ranges	-9<=h<=9; -11<=k<=12; -17<=l<=21
Reflections collected	2187
Independent reflections	2092 [R(int) = 0.1215]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2088 / 0 / 246
Goodness-of-fit on F^2	0.908
Final R indices [I>2 (I)]	R1 = 0.0455 wR2 = 0.1081
R indices (all data)	R1 = 0.1326 wR2 = 0.1622
Absolute structure parameter	-7(4)
Largest diff. peak and hole	0.174 and -0.138 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\ ^2(Fo^2)+(0.1000P)^2+0.0000P]$ where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0102(31)
Extinction expression	$Fc^*=kFc[1+0.001xFc^{2\ 3}/\sin(2\ )]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **126**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	8057(5)	157(4)	-528(2)	44(1)
O(1)	8042(6)	1337(4)	-1527(2)	80(1)
O(2)	8467(5)	-1413(4)	244(2)	62(1)
O(3)	9581(4)	1655(4)	554(2)	58(1)
C(1)	9282(6)	-590(5)	-1518(3)	53(2)
C(2)	9942(9)	-769(7)	-2184(3)	73(2)
C(3)	10754(8)	-1806(7)	-2281(4)	76(2)
C(4)	10910(7)	-2616(6)	-1743(4)	68(2)
C(5)	10244(6)	-2445(5)	-1075(4)	58(2)
C(6)	9432(5)	-1417(5)	-979(3)	45(1)
C(7)	8616(6)	-963(5)	-335(3)	44(1)
C(8)	8406(7)	431(5)	-1238(3)	51(1)
C(9)	7225(6)	948(5)	-54(3)	43(1)
C(10)	5569(6)	561(5)	76(3)	43(1)
C(11)	4735(6)	1074(5)	618(3)	52(2)
C(12)	3200(7)	766(6)	724(3)	61(2)
C(13)	2522(7)	-51(6)	286(4)	66(2)
C(14)	3352(7)	-561(6)	-256(4)	68(2)
C(15)	4872(6)	-251(5)	-361(4)	56(2)
C(16)	8093(5)	1115(5)	637(3)	44(1)
C(17)	8406(5)	2294(5)	943(3)	48(1)
C(18)	8686(6)	2476(5)	1709(3)	51(2)
C(19)	7993(9)	3409(6)	2057(4)	74(2)
C(20)	8222(11)	3576(9)	2783(4)	99(3)
C(21)	9132(10)	2841(10)	3159(4)	94(3)
C(22)	9830(10)	1892(10)	2823(4)	96(3)
C(23)	9582(7)	1715(7)	2098(3)	71(2)

Table 3. Bond lengths [Å] and angles [°] for **126**.

N(1)-C(8)	1.398(7)	C(3)-C(2)-C(1)	117.0(7)
N(1)-C(7)	1.405(7)	C(4)-C(3)-C(2)	121.5(6)
N(1)-C(9)	1.454(7)	C(3)-C(4)-C(5)	121.8(6)
O(1)-C(8)	1.202(7)	C(6)-C(5)-C(4)	116.7(6)
O(2)-C(7)	1.204(7)	C(5)-C(6)-C(1)	121.8(5)
O(3)-C(16)	1.443(6)	C(5)-C(6)-C(7)	130.0(6)
O(3)-C(17)	1.451(6)	C(1)-C(6)-C(7)	108.1(5)
C(1)-C(6)	1.382(8)	O(2)-C(7)-N(1)	125.1(5)
C(1)-C(2)	1.388(8)	O(2)-C(7)-C(6)	129.3(5)
C(1)-C(8)	1.481(8)	N(1)-C(7)-C(6)	105.6(5)
C(2)-C(3)	1.382(11)	O(1)-C(8)-N(1)	124.1(5)
C(3)-C(4)	1.368(10)	O(1)-C(8)-C(1)	130.0(5)
C(4)-C(5)	1.392(10)	N(1)-C(8)-C(1)	106.0(5)
C(5)-C(6)	1.373(8)	N(1)-C(9)-C(16)	110.4(4)
C(6)-C(7)	1.491(8)	N(1)-C(9)-C(10)	113.1(4)
C(9)-C(16)	1.509(7)	C(16)-C(9)-C(10)	111.9(4)
C(9)-C(10)	1.529(7)	C(15)-C(10)-C(11)	119.2(5)
C(10)-C(15)	1.373(8)	C(15)-C(10)-C(9)	121.0(5)
C(10)-C(11)	1.376(7)	C(11)-C(10)-C(9)	119.7(5)
C(11)-C(12)	1.397(8)	C(10)-C(11)-C(12)	120.4(6)
C(12)-C(13)	1.369(9)	C(13)-C(12)-C(11)	119.8(6)
C(13)-C(14)	1.373(10)	C(12)-C(13)-C(14)	119.9(6)
C(14)-C(15)	1.385(9)	C(13)-C(14)-C(15)	120.2(6)
C(16)-C(17)	1.477(8)	C(10)-C(15)-C(14)	120.6(6)
C(17)-C(18)	1.468(8)	O(3)-C(16)-C(17)	59.6(3)
C(18)-C(23)	1.371(9)	O(3)-C(16)-C(9)	114.3(4)
C(18)-C(19)	1.380(9)	C(17)-C(16)-C(9)	122.6(5)
C(19)-C(20)	1.388(10)	O(3)-C(17)-C(18)	116.3(4)
C(20)-C(21)	1.347(12)	O(3)-C(17)-C(16)	59.1(3)
C(21)-C(22)	1.385(13)	C(18)-C(17)-C(16)	122.5(5)
C(22)-C(23)	1.389(10)	C(23)-C(18)-C(19)	118.6(6)
C(8)-N(1)-C(7)	111.7(4)	C(23)-C(18)-C(17)	121.7(6)
C(8)-N(1)-C(9)	123.4(4)	C(19)-C(18)-C(17)	119.7(6)
C(7)-N(1)-C(9)	124.9(4)	C(18)-C(19)-C(20)	120.3(7)
C(16)-O(3)-C(17)	61.4(3)	C(21)-C(20)-C(19)	120.8(8)
C(6)-C(1)-C(2)	121.1(6)	C(20)-C(21)-C(22)	120.0(8)
C(6)-C(1)-C(8)	108.6(5)	C(21)-C(22)-C(23)	119.2(8)
C(2)-C(1)-C(8)	130.2(6)	C(18)-C(23)-C(22)	121.1(7)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **126**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	47(2)	43(2)	43(3)	3(2)	7(2)	6(2)
O(1)	119(3)	62(3)	59(3)	19(2)	23(3)	18(3)
O(2)	86(3)	51(2)	49(2)	10(2)	9(2)	11(2)
O(3)	38(2)	76(3)	61(2)	-9(2)	9(2)	-2(2)
C(1)	53(3)	53(4)	53(3)	-5(3)	6(3)	-5(3)
C(2)	96(5)	74(5)	49(4)	-9(3)	19(4)	-2(4)
C(3)	84(5)	73(5)	72(5)	-15(4)	31(4)	0(4)
C(4)	57(3)	55(4)	90(5)	-23(4)	13(4)	5(3)
C(5)	55(3)	47(3)	71(4)	-9(3)	0(3)	3(3)
C(6)	37(3)	49(3)	48(3)	-6(3)	2(2)	-2(3)
C(7)	42(3)	44(3)	46(3)	0(3)	1(2)	1(2)
C(8)	62(3)	46(3)	43(3)	5(3)	14(3)	1(3)
C(9)	42(3)	43(3)	44(3)	5(2)	4(2)	-2(2)
C(10)	46(3)	45(3)	39(3)	5(3)	1(2)	1(2)
C(11)	48(3)	60(4)	49(3)	-6(3)	6(3)	-3(3)
C(12)	51(3)	75(4)	56(4)	1(3)	11(3)	-1(3)
C(13)	44(3)	70(4)	84(5)	9(4)	-4(3)	-6(3)
C(14)	56(4)	58(4)	91(5)	-14(4)	-12(4)	-5(3)
C(15)	50(3)	56(3)	62(4)	-9(3)	-4(3)	7(3)
C(16)	38(2)	45(3)	48(3)	2(2)	5(2)	-1(2)
C(17)	41(3)	50(3)	52(3)	-1(3)	1(3)	-2(2)
C(18)	47(3)	54(4)	53(3)	-4(3)	1(3)	-8(3)
C(19)	88(4)	68(4)	66(4)	-16(4)	-6(4)	-4(4)
C(20)	125(7)	100(6)	71(5)	-25(5)	11(5)	0(6)
C(21)	90(5)	133(8)	60(5)	-15(5)	-1(4)	-17(6)
C(22)	77(5)	140(8)	69(5)	6(6)	-6(4)	11(5)
C(23)	65(4)	95(5)	54(4)	2(4)	1(3)	10(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **126**.

Atom	x	y	z	U(eq)
H(2)	9843(9)	-216(7)	-2549(3)	87
H(3)	11205(8)	-1957(7)	-2722(4)	92
H(4)	11476(7)	-3299(6)	-1826(4)	81
H(5)	10345(6)	-3000(5)	-711(4)	69
H(9)	7183(6)	1721(5)	-290(3)	52
H(11)	5195(6)	1629(5)	915(3)	63
H(12)	2640(7)	1114(6)	1091(3)	73
H(13)	1501(7)	-259(6)	355(4)	79
H(14)	2893(7)	-1117(6)	-553(4)	82
H(15)	5425(6)	-596(5)	-731(4)	67
H(16)	8033(5)	461(5)	979(3)	52
H(17)	7942(5)	2962(5)	690(3)	57
H(19)	7370(9)	3928(6)	1803(4)	89
H(20)	7742(11)	4203(9)	3014(4)	118
H(21)	9292(10)	2970(10)	3644(4)	113
H(22)	10458(10)	1381(10)	3079(4)	115
H(23)	10031(7)	1070(7)	1872(3)	85

Appendix D

Supplementary data on Figure 4.3 (the X-ray crystal structure for compound (128)).

Crystal data. $C_{23}H_{19}NO_3$, M = 357.39, Orthorhombic , a = 8.482(1), b = 12.239(1), c = 18.205(2) Å , U = 1889.9(3) Å^3, T = 293(2) K, space group $P2_12_12_1$, Z = 4, D_c = 1.256 gcm^{-3}, μ(Mo-$K\alpha$) = 0.083 mm^{-1}, F(000) = 752, 1970 reflections measured, 1904 unique (R_{int} = 0.0065) which were used in all calculations. The final R1, $wR(F^2)$ were 0.0466 and 0.0967 respectively (all data).

Table 1. Crystal data and structure refinement for (**128**).

Identification code	98jmjw2/m.humphries
Empirical formula	$C_{23}H_{19}NO_3$
Formula weight	357.39
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.482(1)Å
	b = 12.239(1)Å
	c = 18.205(2)Å
Volume	1889.9(3) Å^3
Z	4
Density (calculated)	1.256 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	752
Crystal size	0.3 x 0.3 x 0.3 mm
Theta range for data collection	2.00 to 24.96 °.
Index ranges	0<=h<=10; 0<=k<=14; 0<=l<=21
Reflections collected	1970
Independent reflections	1907 [R(int) = 0.0065]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1904 / 0 / 247
Goodness-of-fit on F^2	0.957
Final R indices [I>2 (I)]	R1 = 0.0326 wR2 = 0.0801
R indices (all data)	R1 = 0.0466 wR2 = 0.0967
Absolute structure parameter	0.00
Largest diff. peak and hole	0.122 and -0.113 eÅ^{-3}
Weighting scheme	calc w=1/[^{2}(Fo^2)+(0.0485P)^2+0.2530P] where P=(Fo^2+2Fc^2)/3
Extinction coefficient	0.0131(18)
Extinction expression	Fc*=kFc[1+0.001xFc^2 ^{3}/sin(2)]$^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (**128**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	-2601(2)	1071(2)	-3(1)	43(1)
O(1)	-564(2)	-177(2)	-150(1)	62(1)
O(2)	-4330(2)	2482(2)	-205(1)	70(1)
O(3)	-1288(3)	1868(2)	1337(1)	70(1)
C(1)	-1332(3)	579(2)	-374(1)	46(1)
C(2)	-1167(3)	1190(2)	-1074(1)	46(1)
C(3)	-108(3)	1050(2)	-1639(2)	61(1)
C(4)	-227(4)	1756(3)	-2235(1)	68(1)
C(5)	-1366(4)	2553(3)	-2257(1)	67(1)
C(6)	-2434(4)	2696(2)	-1692(1)	60(1)
C(7)	-2301(3)	1994(2)	-1096(1)	47(1)
C(8)	-3228(3)	1927(2)	-405(1)	47(1)
C(9)	-3238(3)	768(2)	729(1)	42(1)
C(10)	-1925(3)	803(2)	1306(1)	45(1)
C(11)	-2550(3)	559(2)	2069(1)	52(1)
C(12)	-1282(3)	511(2)	2642(1)	50(1)
C(13)	-994(4)	1376(3)	3108(2)	76(1)
C(14)	156(5)	1318(4)	3635(2)	99(1)
C(15)	1046(4)	397(4)	3710(2)	95(1)
C(16)	798(4)	-458(3)	3250(2)	86(1)
C(17)	-359(4)	-401(2)	2722(2)	68(1)
C(18)	-4199(3)	-277(2)	706(1)	43(1)
C(19)	-5825(3)	-214(2)	736(2)	58(1)
C(20)	-6737(4)	-1145(3)	735(2)	72(1)
C(21)	-6051(4)	-2148(3)	700(2)	68(1)
C(22)	-4442(4)	-2230(2)	657(2)	62(1)
C(23)	-3516(3)	-1297(2)	667(1)	54(1)

Table 3. Bond lengths [Å] and angles [°] for **(128)**.

N(1)-C(8)	1.384(3)
N(1)-C(1)	1.407(3)
N(1)-C(9)	1.484(3)
O(1)-C(1)	1.203(3)
O(2)-C(8)	1.211(3)
O(3)-C(10)	1.412(3)
C(1)-C(2)	1.485(3)
C(2)-C(7)	1.377(3)
C(2)-C(3)	1.376(3)
C(3)-C(4)	1.391(4)
C(4)-C(5)	1.373(4)
C(5)-C(6)	1.382(4)
C(6)-C(7)	1.389(3)
C(7)-C(8)	1.486(3)
C(9)-C(18)	1.518(3)
C(9)-C(10)	1.531(3)
C(10)-C(11)	1.516(3)
C(11)-C(12)	1.499(3)
C(12)-C(17)	1.372(4)
C(12)-C(13)	1.378(4)
C(13)-C(14)	1.371(5)
C(14)-C(15)	1.364(5)
C(15)-C(16)	1.356(5)
C(16)-C(17)	1.376(4)
C(18)-C(23)	1.378(3)
C(18)-C(19)	1.382(3)
C(19)-C(20)	1.378(4)
C(20)-C(21)	1.360(4)
C(21)-C(22)	1.371(5)
C(22)-C(23)	1.387(4)
C(8)-N(1)-C(1)	111.3(2)
C(8)-N(1)-C(9)	121.6(2)
C(1)-N(1)-C(9)	127.1(2)
O(1)-C(1)-N(1)	125.5(2)
O(1)-C(1)-C(2)	128.9(2)
N(1)-C(1)-C(2)	105.6(2)
C(7)-C(2)-C(3)	121.6(2)
C(7)-C(2)-C(1)	108.6(2)
C(3)-C(2)-C(1)	129.8(2)
C(2)-C(3)-C(4)	117.3(3)
C(5)-C(4)-C(3)	121.0(3)
C(4)-C(5)-C(6)	121.9(3)
C(5)-C(6)-C(7)	116.8(3)
C(2)-C(7)-C(6)	121.4(2)
C(2)-C(7)-C(8)	107.8(2)
C(6)-C(7)-C(8)	130.8(2)
O(2)-C(8)-N(1)	124.2(2)
O(2)-C(8)-C(7)	129.1(2)

N(1)-C(8)-C(7)	106.7(2)
N(1)-C(9)-C(18)	112.4(2)
N(1)-C(9)-C(10)	110.1(2)
C(18)-C(9)-C(10)	115.7(2)
O(3)-C(10)-C(11)	106.2(2)
O(3)-C(10)-C(9)	109.3(2)
C(11)-C(10)-C(9)	111.6(2)
C(12)-C(11)-C(10)	113.2(2)
C(17)-C(12)-C(13)	117.3(3)
C(17)-C(12)-C(11)	121.0(2)
C(13)-C(12)-C(11)	121.7(3)
C(14)-C(13)-C(12)	121.2(3)
C(15)-C(14)-C(13)	120.5(3)
C(14)-C(15)-C(16)	119.4(3)
C(15)-C(16)-C(17)	120.2(3)
C(12)-C(17)-C(16)	121.6(3)
C(23)-C(18)-C(19)	118.2(3)
C(23)-C(18)-C(9)	122.6(2)
C(19)-C(18)-C(9)	119.2(2)
C(20)-C(19)-C(18)	120.9(3)
C(21)-C(20)-C(19)	120.4(3)
C(20)-C(21)-C(22)	119.7(3)
C(21)-C(22)-C(23)	120.2(3)
C(18)-C(23)-C(22)	120.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for (**128**). The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	46(1)	43(1)	40(1)	2(1)	3(1)	3(1)
O(1)	63(1)	56(1)	67(1)	5(1)	9(1)	17(1)
O(2)	86(1)	72(1)	51(1)	9(1)	9(1)	39(1)
O(3)	92(2)	66(1)	53(1)	3(1)	-3(1)	-36(1)
C(1)	45(1)	44(1)	48(1)	-5(1)	-1(1)	-2(1)
C(2)	46(1)	51(1)	41(1)	-8(1)	-2(1)	-9(1)
C(3)	53(2)	74(2)	57(2)	-13(2)	8(1)	-10(2)
C(4)	68(2)	92(2)	43(1)	-7(2)	12(2)	-24(2)
C(5)	81(2)	78(2)	42(1)	6(1)	-1(2)	-22(2)
C(6)	72(2)	63(2)	44(1)	6(1)	-8(2)	-5(2)
C(7)	54(1)	48(1)	38(1)	-3(1)	-5(1)	-5(1)
C(8)	57(2)	45(1)	39(1)	-2(1)	-2(1)	6(1)
C(9)	45(1)	43(1)	39(1)	1(1)	5(1)	2(1)

C(10)	49(1)	43(1)	44(1)	1(1)	3(1)	-9(1)
C(11)	51(1)	59(2)	45(1)	4(1)	2(1)	-6(1)
C(12)	49(2)	62(2)	38(1)	9(1)	6(1)	-5(1)
C(13)	75(2)	95(2)	57(2)	-20(2)	-3(2)	14(2)
C(14)	89(3)	148(4)	59(2)	-37(2)	-13(2)	5(3)
C(15)	69(2)	162(4)	54(2)	20(2)	-12(2)	-7(3)
C(16)	68(2)	91(3)	99(3)	40(2)	-14(2)	-3(2)
C(17)	66(2)	61(2)	78(2)	13(2)	-4(2)	-8(2)
C(18)	46(1)	46(1)	37(1)	0(1)	1(1)	-5(1)
C(19)	50(2)	60(2)	62(2)	-7(2)	-1(1)	1(1)
C(20)	51(2)	90(2)	77(2)	-13(2)	1(2)	-18(2)
C(21)	79(2)	69(2)	55(2)	-10(2)	6(2)	-30(2)
C(22)	81(2)	47(2)	58(2)	-6(1)	4(2)	-9(2)
C(23)	56(2)	49(1)	58(2)	-3(1)	3(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(128)**.

Atom	x	y	z	U(eq)
H(3)	-708(36)	1966(11)	982(12)	114(15)
H(3A)	656(3)	506(2)	-1623(2)	73
H(4)	476(4)	1688(3)	-2624(1)	82
H(5)	-1420(4)	3010(3)	-2665(1)	80
H(6)	-3205(4)	3235(2)	-1710(1)	72
H(9)	-3978(3)	1350(2)	863(1)	51
H(10)	-1097(3)	278(2)	1177(1)	54
H(11A)	-3305(3)	1119(2)	2204(1)	62
H(11B)	-3102(3)	-135(2)	2059(1)	62
H(13)	-1591(4)	2010(3)	3063(2)	91
H(14)	331(5)	1911(4)	3944(2)	119
H(15)	1816(4)	355(4)	4072(2)	114
H(16)	1412(4)	-1085(3)	3292(2)	103
H(17)	-518(4)	-995(2)	2412(2)	82
H(19)	-6309(3)	467(2)	758(2)	69
H(20)	-7829(4)	-1088(3)	758(2)	87
H(21)	-6670(4)	-2775(3)	704(2)	81
H(22)	-3969(4)	-2914(2)	623(2)	74
H(23)	-2424(3)	-1359(2)	647(1)	65